STUDIES IN NEW NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS

by

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A C K N O W L E D G E M E N T S

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SECTION I.

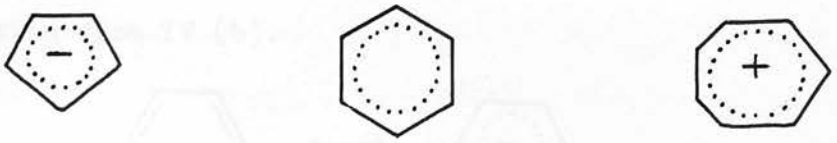
INTRODUCTION AND DISCUSSION.

In 1925 Robinson proposed a basis for the explanation of aromaticity. To quote from his classical paper, (J.C.S.,1925, 127, 1604) "---- these are the chief characteristics of benzenoid systems and here the explanation is obviously that six electrons are available to form a group which resists disruption and may be called the 'aromatic sextet'". Since 1925, our understanding of aromatic compounds has greatly advanced mainly due to the contributions from quantum mechanics. Hückel, using this powerful tool, derived that for a carbocyclic molecule to be aromatic, it must be a planar, conjugated polyolefin with a total of $(4n + 2)$ π electrons ($n = 1,2,3$, etc.)

Within recent years much interest has centred on what are called "non-classical aromatic" systems. As the name implies, these compounds do not possess benzenoid rings alone, yet possess great enough resonance energies and typical reactions to be classed alongside benzene, naphthalene etc., as aromatic compounds.

Molecular orbital calculations of Roberts, Streitwieser and Regan (J.A.C.S., 1952, 74, 4579) confirm the predictions of Hückel that the anion of a five-membered ring and the cation of a seven-membered ring will be more stable than the other possible neutral

or ionic species. This is in agreement with the (4n + 2) rule. These two, with benzene, form a triad (Doering and Knox J.A.C.S., 1954, 76, 3203) which can be formulated as I, II, and III.

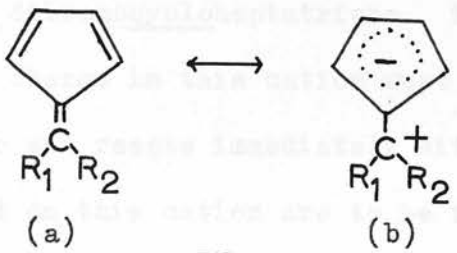


I II III

The circles within each polygon here represent a molecular orbital covering the whole system with as many π orbitals as there are carbon atoms, occupied by a number of electrons equal to the number of carbon atoms plus or minus one, according to the overall charge supported by the system.

Cyclopentadiene, by losing a proton, gives rise to the cyclopentadienyl anion which has six π electrons and the requisite symmetry for aromaticity. The anion is thus greatly stabilised with respect to cyclopentadiene. The resonance energy for cyclopentadiene has been found to be 3 Kcals./mole, no more than 1:3-butadiene whereas the anion has a calculated resonance energy of about 42 Kcals/mole. Goss and Ingold in 1928 attributed the stability of this anion to the distribution of 6 π electrons over five equivalent CH groups. Thus the electronic systems of benzene and the cyclopentadienyl anion are analogous. The significance of the stability of the anion will be seen later when the ylides synthesised are discussed.

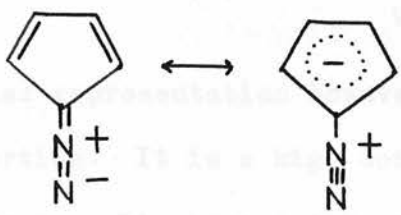
The stability of I has long been recognised in that cyclopentadiene forms stable salts. Cyclopentadiene condenses readily with aldehydes and ketones to form fulvenes IV (a). Their dipole moment, resonance energy and colour suggests that there is an appreciable contribution from IV (b).



(a) (b)

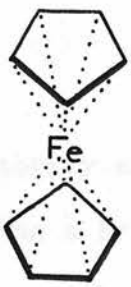
IV

Recently, Doering and Depuy (J.A.C.S., 1953, 75, 5955) prepared diazocyclopentadiene V (a) which is also very stable. Again there must be a significent contribution from V (b). Even more striking is dicyclopentadienyliron, "ferrocene", VI (Kealy and Pauson, Nature 1951, 168, 1039).



(a) (b)

V



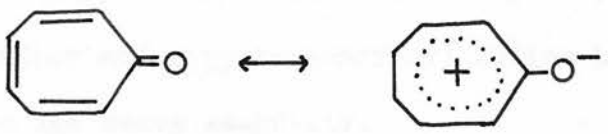
VI

The stability is demonstrated by the fact that it is stable even at 470°C. Ferrocene readily undergoes electrophilic attack. This demonstrates the similarity in behaviour of the C_5H_5 and the benzene rings. The antiprism structure initially suggested by Woodward was proved crystallographically. Only one type of CH

bond was found to be present and the rings are planar and symmetrical. The carbon-carbon bond length was 1.4Å., i.e. of typical aromatic carbon-carbon bond length.

The cycloheptatrienylium cation has been prepared as its bromide by Doering and Knox (J.A.C.S., 1954, 76, 3203) by the distillation of dibromocycloheptatriene. The degree of stabilisation of the positive charge in this cation must be very large for it is soluble in water and reacts immediately with silver nitrate. Structures based on this cation are to be found in tropone and tropolone.

Tropone can formally be written as VII (a).



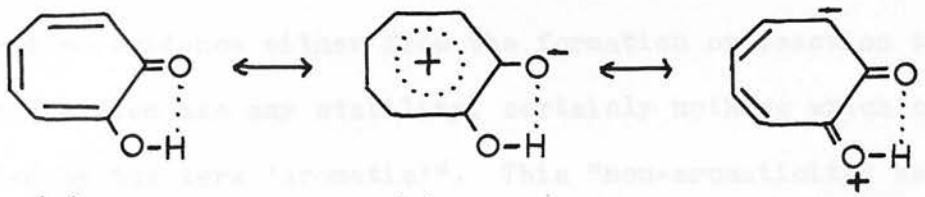
(a) (b)

VII

This formal representation however cannot satisfactorily explain its properties. It is a high boiling liquid, forming a hydrochloride and dipicrate. It shows little carbonyl reactivity and has a dipole moment of 4.3D. Tropone also undergoes electrophilic substitution. Doering and Knox describe tropone otherwise as tropylium oxide VII (b). It must therefore be represented as a resonance hybrid of VII (a) and (b).

Aromatic character is most fully developed in tropolone VIII (a). Here we find no carbonyl activity but rather phenolic properties.

It readily undergoes electrophilic substitution at the α and γ positions. Tropolone has a dipole moment of 3.71D. Tropolone has thus been represented as a resonance hybrid of VIII (a), (b) and (c). (Doering and Knox J.A.C.S., 1952, 74, 5683; Nozoe et al., Nature, 1951, 167, 688).



(a) (b) (c)

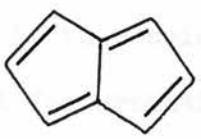
VIII

From the discussion above, it can be seen that sufficient chemical and physical proof has been accumulated to prove that the cyclopentadienyl anion and cycloheptatrienyl cation have considerable resonance energies and hence stability.

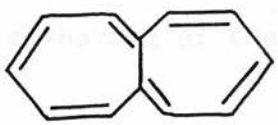
In discussing dicyclic systems derived from cyclopentadiene and cycloheptatriene, it must be emphasised that, just as in the case of tropone and tropolone, there is the possibility of overlap of sp orbitals which will then envelop the whole structure. This does not mean that the electron 'cloud' will be distributed evenly over the whole carbon skeleton. In "non-classical" aromatic systems this is invariably not the case. This fact alone gives rise to the properties peculiar to these systems. This vital feature of the most-studied "non-classical" aromatic systems will be stressed and correlated with the properties of the anhydro salts.

Pentalene, IX, was suggested as a possible aromatic system by

Armit and Robinson (J.C.S., 1922, 828) who later decided against this. They pointed out (J.C.S., 1925, 1604) that there was no possible way in which each ring could attain the stable $\overline{\pi}$ electron "sextet" structure. All possible syntheses of pentalene have so far failed. Blood and Linstead (J.C.S., 1952, 2263) did, however, synthesise 1:2:4:5 - dibenzopentalene. Quoting these authors, "There is as yet no evidence either from the formation or reaction that the pentalene system has any stability, certainly nothing which can be dignified by the term 'aromatic'". This "non-aromaticity" has been attributed by Baker (Progress in Organic Chemistry, vol. III, p.76) to the fact that each ring has a share in only five $\overline{\pi}$ electrons.



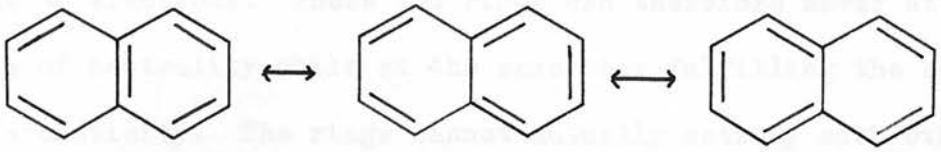
IX



X

Heptalene X was suggested as a possible aromatic compound by Baker et al. (J.C.S., 1945, 258) but subsequent evidence, empirical, experimental and theoretical shows that heptalene is unlikely to exhibit aromatic stability.

An explanation for the failure by pentalene and heptalene to exhibit sufficient stability to permit their isolation by reasonable synthesis can be found by comparison with a bicyclic aromatic compound, naphthalene, which can be represented by XI (a), (b) and (c).



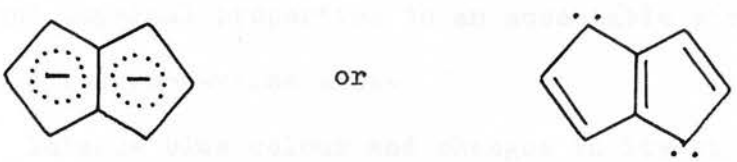
(a) (b) (c)

XI

Structure XI (a) possesses a double bond at the ring junction. There must accordingly be some $\overline{\pi}$ electron density across the bond of ring-fusion. This "segmentation" ensures that of the ten $\overline{\pi}$ electrons available to the system, each segment (ring) has an equal share and effectively a full complement of six $\overline{\pi}$ electrons-four unshared and two shared.

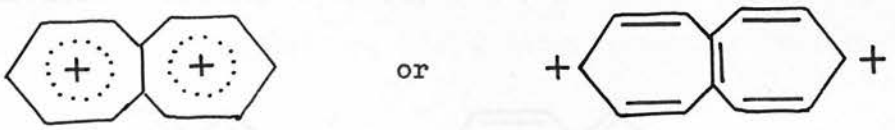
It is however impossible to write any purely covalent structure for pentalene or heptalene with a double bond at the junction of the two rings. It is considered that this sharing of two $\overline{\pi}$ electrons is essential for aromaticity.

In monocyclic systems it has been seen that the stable conditions are the triad I, II and III. In bicyclic systems, naphthalene represents a stable fusion of two neutral benzene rings. The equivalent condition for two five-membered rings is



with a total of ten $\overline{\pi}$ electrons. This is a dianion whereas IX has

eight π electrons. These two rings can therefore never attain a state of neutrality while at the same time fulfilling the conditions for aromaticity. The rings cannot mutually satisfy each other . Similarly, the equivalent condition for two seven-membered rings is:-



and since this is a dication, the same argument applies. Heptalene has twelve π electrons, the dication ten. Each member of the triad can thus be fused with either of the other two and produce an aromatic compound whereas only the six-membered, neutral ring can be fused with a similar ring and be aromatic.

The third member of the series is azulene XI which contains fused five- and seven-membered rings. It is certainly aromatic. Derivatives of this compound have been known for many years but its structure and properties have been revealed comparitively recently. This hydrocarbon presents difficulties in the relationship of chemical and physical properties to an acceptable structure. The salient physical properties are:-

(1) Intense blue colour and changes in its visible spectrum on substitution.

(2) Dipole moment.

(3) Basicity.

The chemical properties are:-

(1) Electrophilic substitution at positions 1 (3).

(2) Nucleophilic substitution at positions 4 (6,8).

None of these characteristics can be explained on the basis of purely covalent structures XI (a) and (b).

(a) (b)

XI

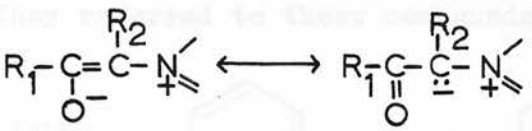
Stafford and Reid (Chem. and Ind., 1954, 277) have pointed out a close parallelism between the azulenes and anhydro salts. It will therefore be most relevant at this point to give an account of the anhydro salts in order that features common to them and azulene may be discussed together and the results related to the objects and results of this research.

Anhydro salts are derived from a cationic compound possessing an acid group or a group capable of acting as an acid, by the loss of a proton. The cation is most frequently $=\overset{+}{N}=$ but can also be $=\overset{+}{P}=$, $=\overset{+}{S}-$ or $=\overset{+}{O}-$. The anionic centre may be derived from -OH (phenolic and enolic), -NH-, =NOH, =CH- and the aci-nitro group. All anhydro salt formation can be expressed in the form of a general equation:-

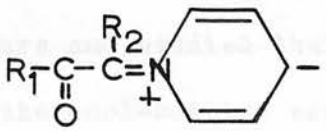
$$R\overset{+}{X}\underset{Hal^-}{-YH} \longrightarrow R\overset{+}{X}\underset{OH^-}{-YH} \longrightarrow R\overset{+}{X}-\overset{-}{Y}\cdot H_2O$$

where X is the cationic centre, YH the acidic centre. They are therefore derived from an hydroxonium base by the elimination of water, hence their name.

Of particular interest in these studies are enol - and C$^-$-betaines. ("Betaine" is synonymous with "anhydro salt"). These are related in that, in the enol-betaines, the following mesomeric forms are possible:-



i.e. the negative charge may formally be written on either the oxygen or carbon atoms. It is understood that if the nitrogen atom is part of, for example, a pyridine ring, then there will be contributions from structures as XII.



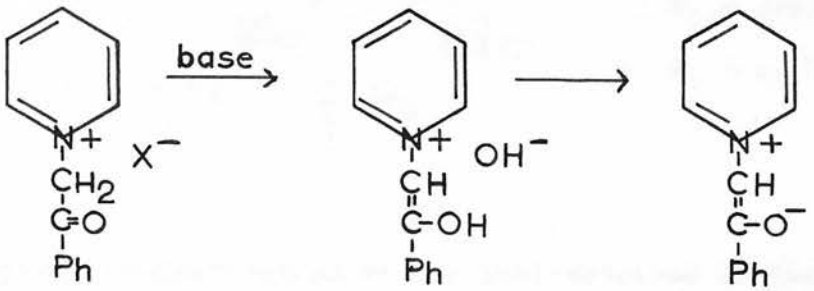
XII

In the C$^-$-betaines, the negative charge may only be associated with one or more carbon atoms. Jessop and Ingold (J.C.S., 1929, 2357) proposed the name "Ylidide" and Wittig (Ann., 1944, 555, 133) the name "Ylide" for such compounds which is intended to suggest the co-existence of covalent (yl-) and ionic (-ide) characteristics. This means that the enol-betaines are also C$^-$-betaines although the

reverse is not true.

It was Bamberger (Ber., 1887, 20, 3338) who initially noticed that if phenacyl pyridinium salts were treated with alkali, coloured intermediates were formed. He was, however, unable to isolate the compounds responsible.

Krollpfeiffer and Muller (Ber., 1933, 66, 740) obtained the first enol-betaine by mild alkali treatment of phenacyl pyridinium halides, XIII. They referred to these compounds as "anhydro-bases".

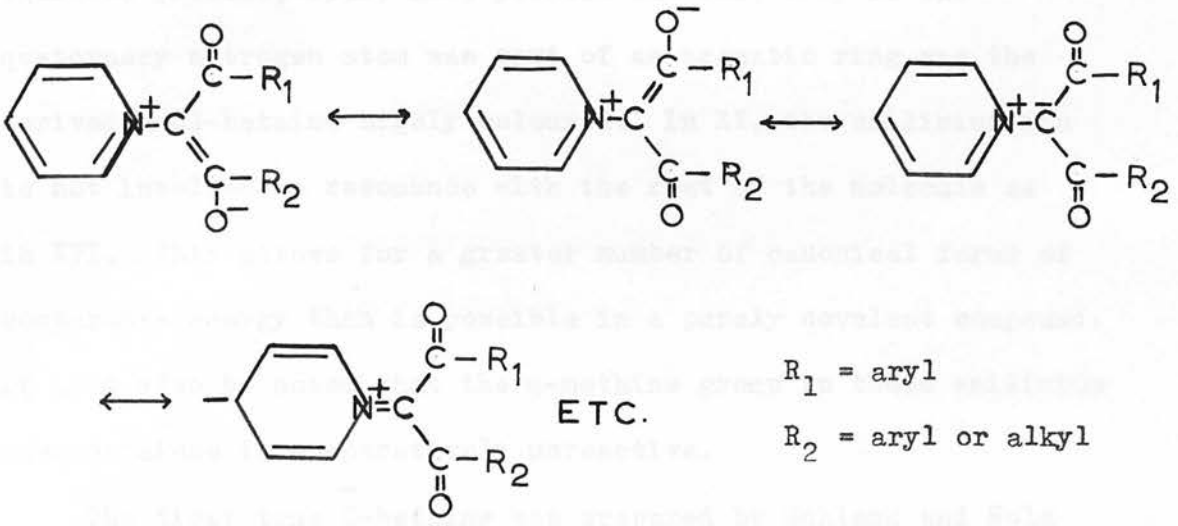


XIII

Krohnke took up the study of what he called the enol-betaines and proved their structure and studied their properties. The outstanding feature of the enol-betaine was found to be the great reactivity of the α-methine group. This carbon atom undergoes substitution reactions readily, e.g., by an acyl group on reaction with acyl halides. These enol-betaines are also strongly basic and tend to form hydrates.

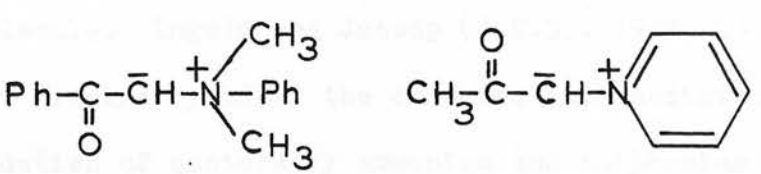
The products obtained by replacement of an hydrogen atom by an acyl group have, however, quite different properties. These compounds XIV, show great stability, higher melting point and solubility in polar solvents. These properties, together with a complete lack

of basicity, were recognised as being due to increased mesomeric possibilities.



XIV

Another characteristic of the enol-betaines is their colour. They are very often highly coloured, yellow, yellow-red or red compounds. One stipulation must be that there is a separation of charge within the molecule. As will be seen later, this need not be a formal separation, nor a localisation to any one atom. But this is not the only requirement. XV is colourless whereas XVI is yellow.

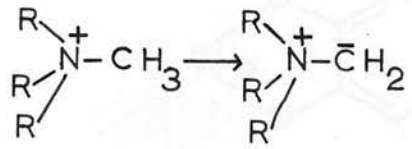


XV XVI

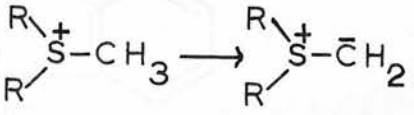
Krohnke (Ber., 1935, 68, 1177) attributed the colour to the extended conjugated system and the polar nature of the molecule. Stafford (J.C.S., 1952, 580) pointed out that only if the quaternary nitrogen atom was part of an aromatic ring was the derived enol-betaine highly coloured. In XV, the anilinium ion is not involved in resonance with the rest of the molecule as in XVI. This allows for a greater number of canonical forms of comparable energy than is possible in a purely covalent compound. It must also be noted that the α-methine group in these anilinium enol-betaines is comparatively unreactive.

The first true C-betaine was prepared by Schlenk and Holz (Ber., 1916, 49, 603; 1917, 50, 274). This was the red triphenyl tetraalkyl ammonium betaine.

Krollpfeiffer and Schneider (Ann., 1937, 530, 34) noticed that the action of alkali on fluorenyl-9-pyridinium salts produced a deep blue colour. By analogy with betaine formation, they linked this with the formation of an ylide. The effect of the pyridine ring is again demonstrated in that trimethyl-ammonium-9-fluorenylide is only orange-red, (Wittig, Ann., 1944, 555, 134). However, the betaine from diphenylmethylpyridinium bromide is colourless. This can be attributed to the non-planarity of the molecule. Ingold and Jessop (J.C.S., 1929, 2357; 1930, 713) first examined ylides, the coloured intermediates formed in the degradation of quaternary ammonium and sulphonium hydroxides, XVII and XVIII.

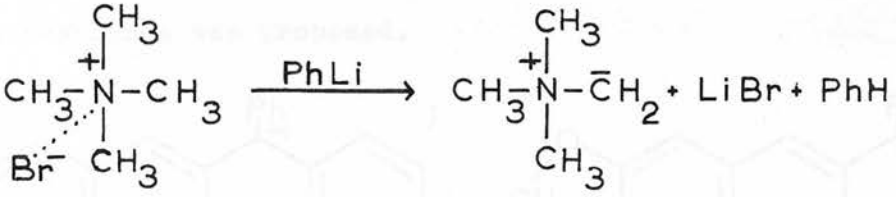


XVII

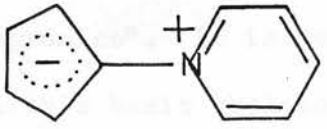


XVIII

Wittig, in a series of papers, (Ann., 1944, 555, 133; 1945, 557, 193; 1949, 562, 187) has shown that compounds of the type XVII and XVIII can be readily synthesised by the action of lithium phenyl on the quaternary compound, e.g.,

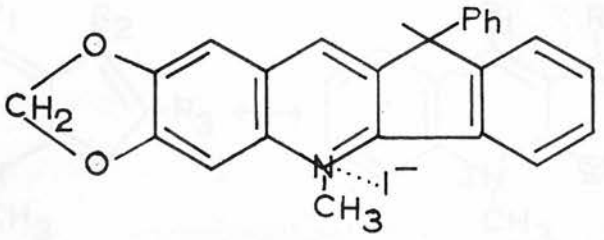


The ylide, XIX, is claimed to have been prepared by Lloyd and Sneezum (Chem. and Ind., 1955, 1221) from dibromocyclopentene and pyridine. It appears to have all the properties and intense colour of a C-betaine.



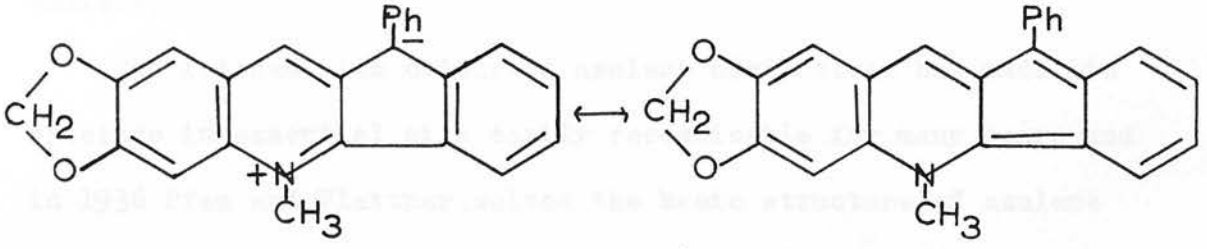
XIX

The first example of an ylide derived from a five membered ring fused to a pyridine ring was described by Armit and Robinson (J.C.S., 1925, 1604). They synthesised XX and obtained the anhydro salt by treatment with alkali.



XX

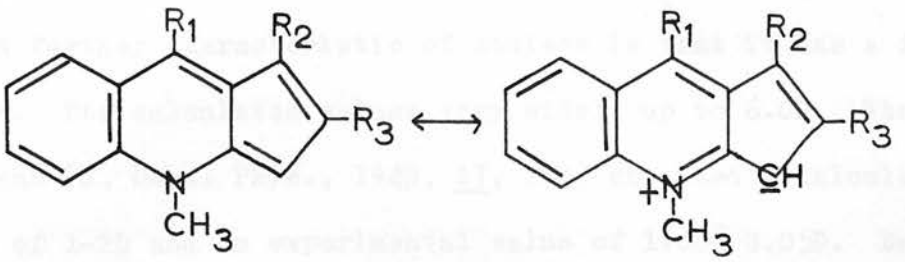
The anhydro salt was a green solid. Armit and Robinson effectively proposed that the anhydro salt should be represented as a resonance hybrid of the structures XXI and XXII, although their paper appeared before resonance was proposed.



XXI XXII

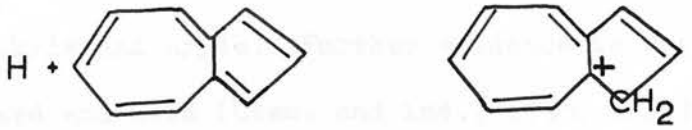
Quoting these authors, "The tendency to aromatic sextet formation and to neutralisation of the charges work in opposite direction and must reach some compromise". It is now suggested that these compounds which contain this basic skeleton of a fused cyclopentadiene ring with a quaternised pyridine ring are iso-electronic with and have comparable properties to azulene.

The following compounds XXIII (R_1 = COOMe, R_2 = H, R_3 = C_6H_5), XXIV (R_1 = H, R_2 = H, R_3 = C_6H_5), XXV (R_1 = COOMe, R_2 = C_6H_5, R_3 = C_6H_5) and XXVI (R_1 = H, R_2 = C_6H_5, R_3 = C_6H_5) have been synthesised.



In each case, the anhydro salt was intensely blue in colour. There must therefore be a very close relationship between these betaines and azulene and in the succeeding pages an attempt will be made to explain the nature of these compounds by direct comparison with azulene.

The intense blue colour of azulene derivatives has made its presence in essential oils easily recognisable for many years and in 1936 Pfau and Plattner solved the basic structure of azulene and they described the synthesis of the parent compound in 1937 (H.C.A., 1937, 20, 224). Sherndal (J.A.C.S., 1915, 37, 1537) discovered that the azulenes could be extracted into mineral acids and were regenerated on dilution. Plattner, Heilbronner and Weber (H.C.A., 1952, 35, 1036) considered that this was not merely solution of the azulenes in the acids but a reversible, chemical reaction which they formulated as



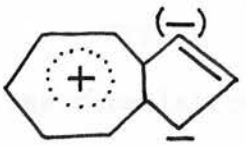
This was an important step forward in the understanding of the structure of azulene.

A further characteristic of azulene is that it has a dipole moment. The calculated values vary widely up to 6.0D. Wheland and Mann (J. Chem. Phys., 1949, 17, 264) obtained a calculated value of 1-2D and an experimental value of 1.00$\pm$ 0.05D. Due to the high light-absorbing power of azulene, the standard optical method could not be applied to determine the electronic polorisation and so the experimental value was based on the assumption that the molecular refraction of azulene was the same as that of naphthalene. This is unlikely to be justified and the dipole moment may well be higher than 1.0.D.

Brown in 1948 (Trans. Farad. Soc., 1948, 44, 984) predicted that electrophilic substitution would take place at position 1 (3). This was verified by Anderson, Nelson and Tazuma (J.A.C.S., 1953, 75, 4980) who showed that the acetyl, nitro and halogeno azulenes, obtained by electrophilic substitution were 1-substituted compounds. Disubstitution occured readily to give 1:3-disubstituted azulenes. Guiazulene moreover is acetylated directly by acetyl bromide in the absence of any catalyst (Galloway, Reid and Stafford, Chem and Ind., 1954, 724). Nucleophilic substitution has been shown to occur at positions 4 and 8. Hafner and Weldes (Ang. Chemie, 1955, 67, 302) obtained 4 and 8 alkyl and aryl azulenes by the use of aluminium alkyls and aryls. Further evidence is provided by Stafford, Ward and Reid (Chem. and Ind., 1955, 1258) from the reaction of azulene with sodamide.

These are the experimental facts concerning azulene which require an explanation. These may be compared and contrasted with the properties of the enol- and $\bar{C}$-betaines described above namely, high colour, basicity, dipole moment and ready substitution.

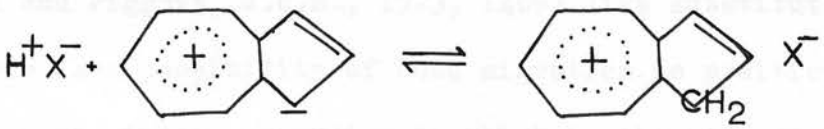
It was shown earlier that the cyclopentadienyl anion and the cycloheptatrienyl cation show typical stability and aromatic properties. In azulene there is a fusion of five and seven-membered rings. It was also suggested that a prerequisite for a bicyclic system to show aromaticity was some sharing of two $\bar{\pi}$ electrons at the common bond. The only way in which both are satisfied in azulene is that there is an electron sharing between the seven- and five-membered rings. Each has now four $\bar{\pi}$ electrons and a share in two others, effectively six $\bar{\pi}$ electrons. Here we have a system of isoelectronic structure with naphthalene. The properties are however vastly different and the explanation must lie in the fact that this electron transfer has occured. Although the molecule as a whole is electrically neutral, there must be a separation of charge to account for the observed dipole moment. Anderson, Nelson and Tazuma, (J.A.C.S., 1953, 75, 4980) represented the reacting structure of azulene as XXVII,



XXVII

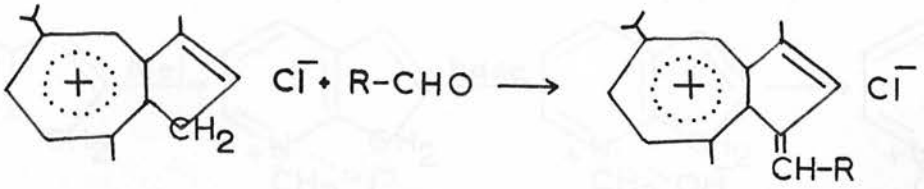
whereas Stafford and Reid (Chem. and Ind., 1954, 277, 724) concluded that azulene is best represented in the ground state as a resonance hybrid of the two classical, covalent structures together with the betanoid structures included in the formula XXVII. In all, nineteen canonical forms can then be written for azulene, six of these showing some π electron density at the ring junction bond.

This formulation gives an explanation of the properties of azulene. The deep colour is associated with the cationic and anionic nature of the two aromatic rings and the negative charge associated with one or more carbon atoms. As a result of this charge separation, azulene has a dipole moment. Since negative character is most highly developed at carbon atoms 1 and 3, electrophilic substitution will take place at these positions. The basicity of azulene shows how readily an electron pair can be localised and shared with the hydrogen ion (electrophilic reagent) and also the stability of the cycloheptatrienylium cation, i.e.

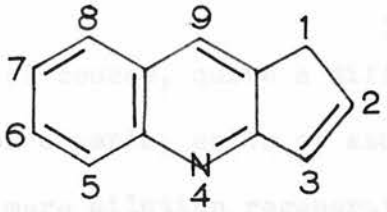


XXVIII

and in accordance with the formulation XXVIII, the salts of azulene possess a reactive methylene group which condenses with aldehydes to give unstable fulvene - like compounds, for example, in guiazulene (Galloway, Reid and Stafford, Chem. and Ind., 1954, 724)

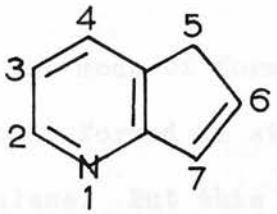


It is appropriate at this point to indicate the nomenclature and numbering to be used for the compounds synthesised and to be discussed. There are several systems in use. Those in current use in British Journals are XXIX and XXX and these will be used throughout.



β-quinindine

XXIX

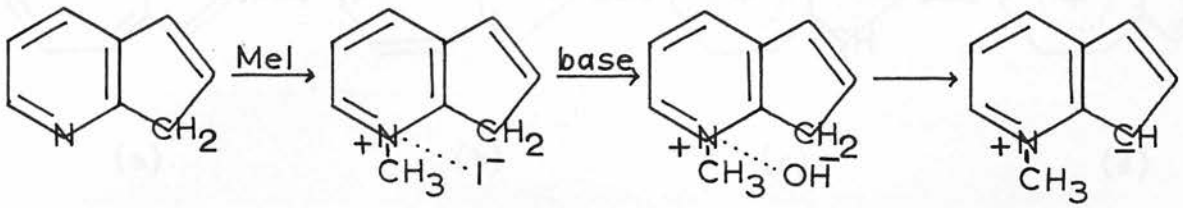


β-pyrindine

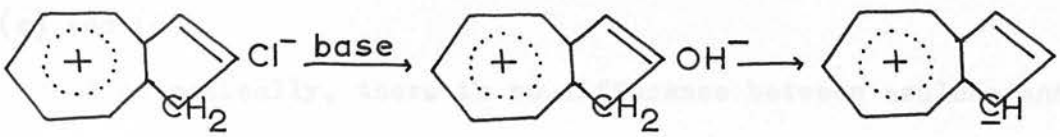
XXX

These substances are represented as possessing a 2:3 and 6:7 double bond respectively. They are typical "triad systems" (Ingold and Piggott, J.C.S., 1923, 1469) like substituted indenes and there is a possibility of bond migration to positions 1:2 and 5:6 respectively according to which is the more stable.

In the formation of the anhydro salts from XXIX and XXX, a direct comparison can be made with azulene. The scheme for β-pyrindine is:-



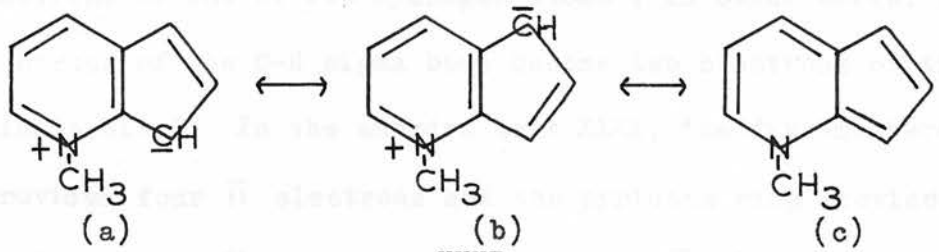
This must be compared with azulene as formulated in XXVIII.



XXVIII

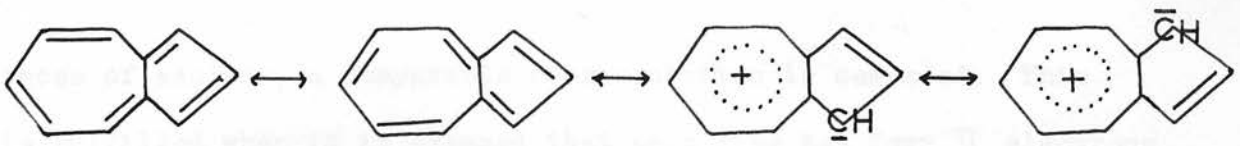
There is of course, quite a difference in the mode of formation since, for example, salts of azulene are only formed in strong acid and mere dilution regenerates the azulene. But this is only a matter of degree.

It was shown that XXVII was considered to be one of the contributing structures to the resonance hybrid of azulene. There was also a purely covalent canonical structure XI. In this respect, the anhydro salts derived from pyrindines and quinindines are analogous.



XXXI

XXXI should be compared with XXXII.



(a) (b) (c) (d)

XXXII

Here XXXI (c) is uniquely covalent and comparable to XXXII (a)and (b), XXXI (a) and (b) also being comparable with XXXII (c) and (d).

Electronically, there is no difference between azulene and the anhydro salts. For aromaticity, it has been shown that cyclopentadiene must be associated with a negative charge. Abstraction of a hydrogen cation from a carbon atom can be considered as being equivalent to an electron pair on that atom. Cyclopentadiene has four $\overline{\pi}$ electrons from two multiple bonds. Removal of a hydrogen ion provides this electron pair which is absorbed into the molecular orbital giving a total of six $\overline{\pi}$ electrons in the cyclopentadienyl anion. This can then be considered from a different point of view. Goss and Ingold (J.C.S., 1928, 1268) state "In regard to its ability to provide electrons for the stable sextet, cyclopentadiene can do so only by the appropriation of the electrons of one of its hydrogen atoms"; in other words, the two electrons of the C-H sigma bond become two electrons of the molecular orbital. In the anhydro salt XXXI, the five-membered ring provides four $\overline{\pi}$ electrons and the pyridine ring provides six $\overline{\pi}$ electrons. This gives a total of ten $\overline{\pi}$ electrons as in naphthalene and azulene. Since the properties are so similar to

those of azulene, a comparable representation is demanded. This is fulfilled when it is assumed that each ring has four $\overline{\pi}$ electrons with a share in two others at the bond of fusion of the two rings. In this way, as described for azulene, each ring has, in effect, the desired sextet.

The derivation of the electronic state of these anhydro salts is, however, at variance with that proposed by Baker ("Concept of Aromaticity" in "Perspectives in Organic Chemistry"edited by Sir A. Todd). Baker states, "------and the sextet is made up in the five-membered ring by the acquisition of an extra electron------ derived from the nitrogen atom which has two $\overline{\pi}$ electrons".

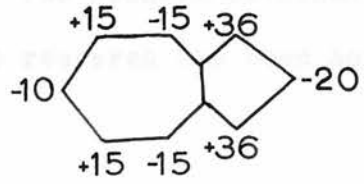
The nitrogen atom of the pyridine ring has a lone pair of electrons. In quaternisation, there is an electrophilic attack by a methyl cation on this electron pair. Although this C-N bond is in the plane of the pyridine ring, these two electrons are localised in this sigma-bond, with the nitrogen atom now sharing its lone pair of electrons and thus possessing a positive charge. This leaves three electrons; two are involved in two C-N bonds of the pyridine ring while the third $\overline{\pi}$ electron is involved in the molecular orbital. The conversion to the anhydro salt involves the already existent pyridine sextet with the development of a new electron pair by C-H heteropolar scission which ascends joining the pair from the double bond and uniting with the sextet.

All the anhydro salts obtained from β-quinindine derivatives

were intensely blue. In common with the azulenes, they formed 1:3:5 trinitrobenzene (T.N.B.) complexes which were beautifully crystalline and usually stable derivatives. Just as phenyl azulenes often give no T.N.B. complex or unstable complexes, it was found in the case of XXV, which was readily obtained in a crystalline state, that difficulty was found in recrystallising the T.N.B. derivative. Dissociation was found to occur unless a saturated solution of the complexing reagent was employed as solvent. A characteristic feature of the $\bar{C}$-betaines is their instability, indeed, some have but a fleeting existence. Azulene and its derivatives suffer similarly. When other groups are present which can help to absorb the negative character, then the stability is greatly enhanced. The instability of the $\bar{C}$-betaines has been attributed to the susceptability of the carbanion to atmospheric oxidation. (Saxena, Ph.D. Thesis, Edinburgh University, 1955). Indeed, fluorenone was isolated from the photochemical oxidation of pyridinium-9-fluorenylide. Solutions of the β-quinindine anhydro salts turned from blue to yellow within 24 hours and then became very dark. Strong sunlight appears to accelerate the decomposition. The betaine XXV, however, appears to be indefinitely stable in the solid state.

The blue quinindine betaines are basic and form yellow salts with dilute acid possessing an intense blue fluorescence in solution. Their salts revert in part to the blue state when suspended in water or ethanol.

Many derivatives of azulene are known and their spectra have been correlated. Alkyl substituents in azulene invariably produce a bathochromic displacement in the ultra-violet absorption spectrum which is expected of aromatic compounds in general but mono-alkyl azulenes have unusual visible absorption spectra. There is a displacement relative to azulene, hypsochromic or bathochromic, dependent on the position of substitution as shown in XXXIII, but comparitively independent of the nature of the alkyl group.



XXXIII

Since only four of the comparable anhydro salts have been prepared, generalisations are impossible. A comparison of interest would be between the anhydro salts and the substituted 5:6-benzazulenes. 2-phenylazulene and 5:6-benzazulene show characteristic change in the ultra-violet from azulene. This indicates that benzene rings have a profound effect on the system. There is however one feature common to both these anhydro salts and azulene; they both show a band at c.550-600 mμ of medium strength in the visible spectrum and that in acid solution, this band disappears.

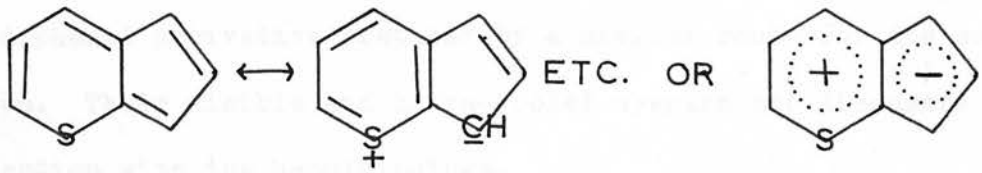
The spectra are given in the next section together with those

of their precursors and relevant reference compounds.

The object of this research was thus attained. On theoretical grounds, a system was derived which should show properties similar to those of azulene. Experimental evidence was desired to prove or disprove whether a -CH=CH- in azulene could be replaced by the group =NR while still retaining those properties peculiar to the azulenic system. Considerable difficulties were encountered in the synthesis of the hitherto unknown pyrindine and quinindine compounds and it has only been possible to obtain the desired system in more complex derivatives. The results obtained show that the theoretical reasoning behind this research has been borne out.

These arguments put forward for the similarity between azulene and the β-quinindines and pyrindines apply equally well to both the oxygen and sulphur analogues. Two recent publications show that the -CH=CH- grouping in the seven-membered ring of azulene may also be replaced by -O- or -S-.

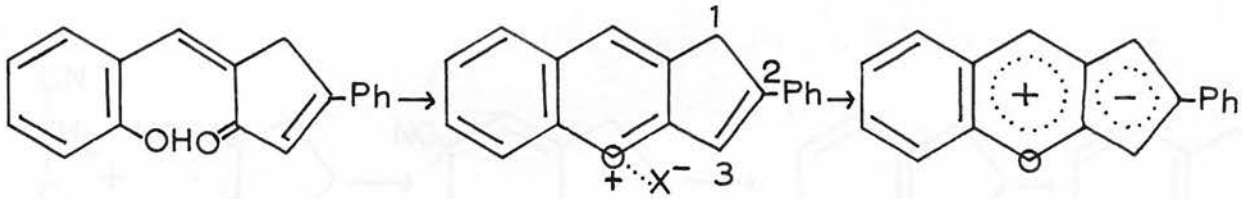
Mayer (Ang. Chemie, 1957, 69, 481) has been investigating the sulphur anologues. Although no experimental details are given, he claims to have synthesised the parent compound and the 1:2-benzo derivative from 2-carbethoxy-1-cyclopentanone.



Mayer proposes the name "thialenes" for these compounds which is intended to convey their similarity to the azulenes. As in the β-quinindines, betainoid as well as purely covalent structures must be written, as above, to account for their properties.

In 1951, Brown (J.C.S., 1951, 2670) and Dauben and Ringold (J.A.C.S., 1951, 73, 876) pointed out the similarity between tropone and γ-pyrone. Mayer has extended this and shown that α-pyrone, α-and γ-thiapyrones all show the same properties as tropone and further, that the oxygen atom in the thiapyrones can be replaced by sulphur without loss of typical tropone character.

Boyd (Chem. and Ind., 1957, 1244) has succeeded in synthesising some of the oxygen analogues of β-quinindine. By the following reactions, 2-phenylbenzocyclopentapyran was obtained:-

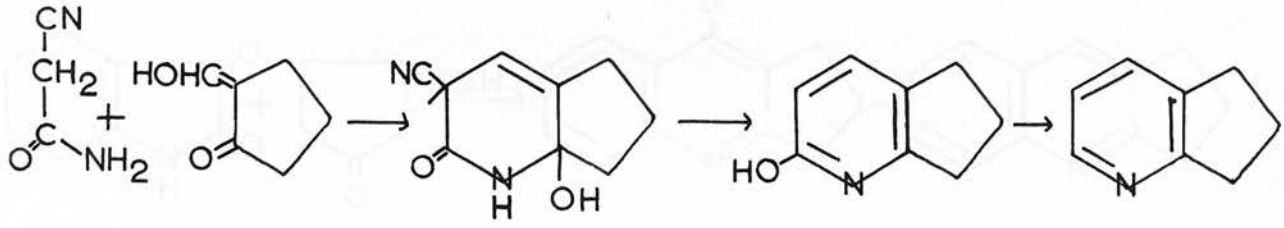


This compound is very stable and highly coloured. Boyd claims that it shows some resemblance to azulene both in its chemical properties and its ultra-violet and visible spectrum. This compound is of particular interest since the nitrogen analogue has been synthesised. The synthesis of this compound was repeated and the 1:2-diphenyl derivative prepared by a similar route for the same reason. Their visible and ultra-violet spectra are discussed in connection with the β-quinindines.

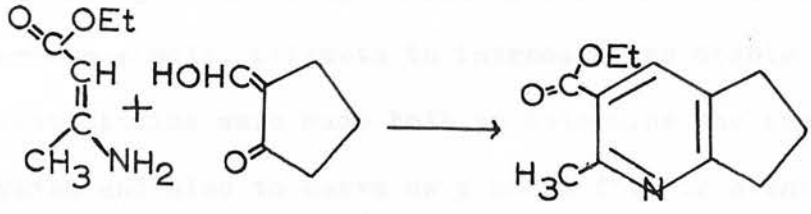
DISCUSSION OF EXPERIMENTAL

The majority of syntheses described for pyrindines and quinindines start from cyclopentanone or a substituted cyclopentanone and lead to the dihydro compound. Only one reference exists to the synthesis of a pyrindine or quinindine in which the double bond in the five-membered ring is present (Ramirez and Paul, J.A.C.S., 1955, 77, 1035). A comprehensive review of the pyrindines, quinindines and related compounds is given by Elderfield and Losin, (Heterocyclic Compounds, Volume 3, edited by Robert C. Elderfield) and only the syntheses relevant to the experimental are discussed.

Hydroxymethylenecyclopentanone has been used to prepare pyrindines by Schemes I, due to Thompson (J.A.C.S., 1931, 53, 3160) and II, due to Basu. (Ann., 1937, 530, 131).



Scheme I

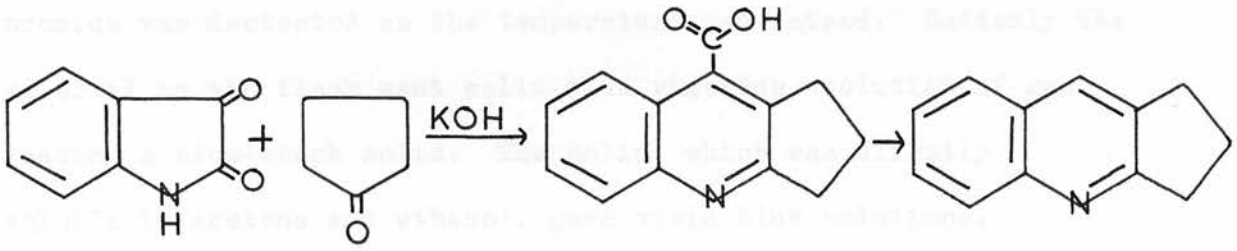


Scheme II

The best preparation of the parent compound is that of Prelog and Szpilfogel (H.C.A. 1945, 28, 1684) involving the condensation of ethyl 2-amino-1-cyclopentene-1-carboxylate with diethyl oxalate in the presence of sodium ethoxide. 2:4-dihydroxydihydropyrindine-3-carboxylate is formed in good yield and gives the parent compound by standard transformations.

Stobbe (Ber., 1902, 35, 1445) discovered that 1:5-diketones on treatment with hydroxylamine hydrochloride yielded pyridine derivatives. He extended this method to prepare 2:4-diaryl pyrindines by reacting the 1:5-diketone resulting from the addition of cyclopentanone to chalcone with hydroxylamine hydrochloride.

In the β-quinindine series, the most successful previous synthesis is that of Borsche. (Ann., 1910, 377, 120; Ber., 1908, 41, 2203).



Since the starting materials are readily available and the reaction scheme simple, attempts to introduce the double bond into the dihydroquinindine were made both to determine the properties of this system and also to serve as a model for the eventual preparation of pyrindine.

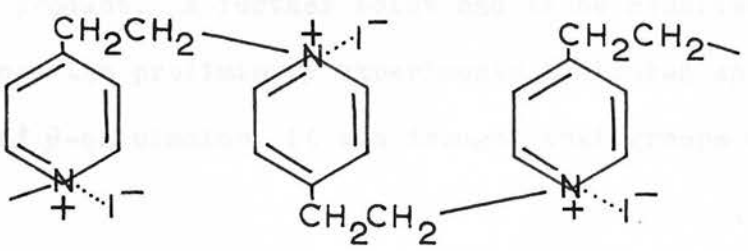
Prelog and Szpilfogel attempted to dehydrogenate β-pyrindine

directly by heating it with sulphur and selenium. In both cases, only starting materials were isolated from the reactions. When 2:3-dihydro-β-quinindine was heated with sulphur, a little starting material was recovered. Chromatography on alumina produced only tars which could not be purified and from which no crystalline derivative could be prepared.

Subsequent work has shown that the stability of the β-quinindines appears to be greatly enhanced by the presence of a carbomethoxy group in position 9. Further attempts were therefore made to dehydrogenate the ester by conventional chemical methods.

Methyl dihydro-β-quinindine-9-carboxylate was treated with N-bromosuccinimide in carbon tetrachloride solution. The bromo derivative was isolated in the usual manner. It was decided to purify the product by distillation under high vaccuum. Hydrogen bromide was dectected as the temperature was raised. Suddenly the material in the flask went solid with vigorous evolution of gas leaving a blue-black solid. The solid, which was slightly soluble in acetone and ethanol, gave vivid blue solutions.

A similar reaction is described by Meisenheimer (Ann., 1920, 420, 190) who in attempting to prepare 4-vinylpyridine, found that 4-iodoethylpyridine yielded a polymer on heating of the suggested structure,



A similar formulation can be given to the blue polymer obtained above but with a quinindine terminal group and this was confirmed by analysis. Meisenheimer found that the desired reaction took place by treating 4-iodethylpyridine with alcoholic potassium hydroxide. This method only produced tars in the case of the dihydroquinindine derivative.

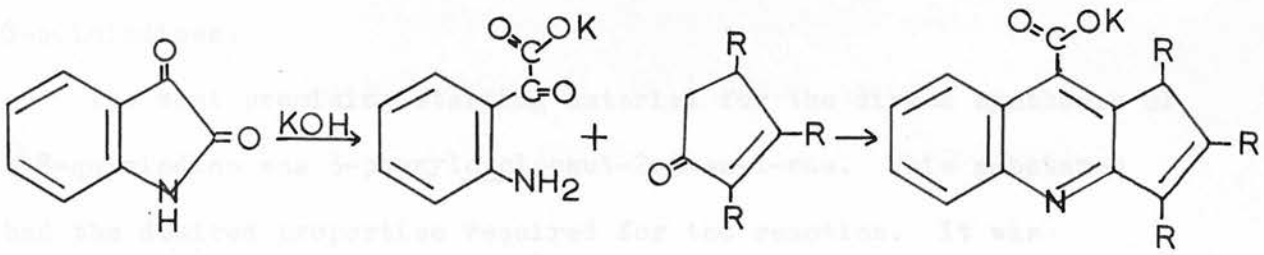
The bromo compound was characterised by the formation of a pyridinium bromide. Krohnke, in a review on the pyridinium salts (Angew. Chem., 1953, 65, 605), cites several cases where these salts decompose into pyridine hydrobromide and the unsaturated derivatives by distillation under vaccuum. This method was unsuccessful in the case of the β-quinindine derivative. Pyridine was detected in the cold trap and the residue appeared again as a blue polymer.

These preliminary experiments indicated that there would be considerable difficulties in introducing a double bond in the five-membered ring. It also appears that β-quinindine is not a very stable substance and readily polymerises.

An alternative approach to the problem entails the use of cyclopentenone, or one of its derivatives, as starting material. Providing the intended synthetic route did not involve reductive methods, then this unsaturated five-membered ring would be part of the final product. A further point had to be considered however. Since the preliminary experiments indicated an inherent instability of β-quinindine, it was thought that groups capable

of conjugating with the double bond of the five-membered ring would facilitate the synthesis.

The most direct synthesis in which a cyclopentenone could be employed appeared to be the Pfitzinger quinoline synthesis. The general scheme for the Pfitzinger reaction with a cyclopentenone would be,



As generally performed, the reaction is carried out by dissolving the isatin in 30% sodium or potassium hydroxide solution which results in the formation of the salts of isatic acid. An alcoholic solution of the α-methylene ketone is added and the condensation carried out directly without the isolation of the isatic acid. (Pfitzinger, J. prakt. chem., 1902, 66, 263 and earlier papers). This concentration of alkali often causes the resinification of aldehydes and the simpler ketones and in these cases, the oxime of the carbonyl compound may be substituted with good results.

Only one reference appears in the literature which describes the application of the Pfitzinger reaction to α-β-unsaturated ketones. John (J. prakt. Chem., 1927, 117, 214) describes the condensation of isatin and benzylidine acetone. This was repeated as a model experiment and it was found that the major product was

a viscous mass which slowly set to a solid. It was non-acidic and not the desired product. Only a very small yield of 2-styrylquinoline-4-carboxylic acid was obtained by laborious extractions with alkali and subsequent acidification with acetic acid. For comparison, the acid was esterified with ethanol/sulphuric acid. The ester was highly fluorescent in solution as are the β-quinindines.

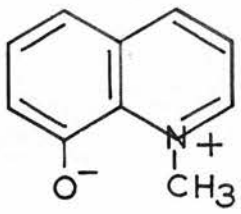
The most promising starting material for the direct synthesis of a β-quinindine was 3-phenylcyclopent-2:3-en-1-one. This substance had the desired properties required for the reaction. It was readily obtainable by the action of ω-bromoacetophenone on sodio-acetoacetate followed by cyclisation and decarboxylation in caustic soda solution. (Borsche and Menz, Ber., 1908, 41, 194; Mousseron and Rouzier, Bull. Soc., 1953, 190).

The condensation with isatin was carried out in the usual manner. The resulting yellow-green acid was insoluble in most organic solvents but in dilute solutions an intense blue fluorescence was observed. The acid was found to crystallise from pyridine solution in fine, yellow needles. The yield, compared to the reaction with benzylidine acetone, was very good (70%).

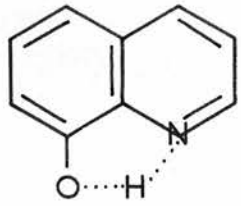
The reaction scheme III was carried out. XXXIII was suspended in ether and treated with an etherial solution of diazomethane. The acid slowly dissolved giving a dark green solution. Chromatography on alumina showed the presence of two products, the colourless methyl ester, XXXIV, which was crystallised and analysed and the blue anhydro salt, XXIII, characterised as its T.N.B. complex.

The infra-red spectrum of the acid suggested that it exists as a zwitterion. Since the ester does not react with diazomethane to give the betaine, this also indicates the same and shows that N-methylation must precede O-methylation in the formation of the blue betaine. N-methylation having occured, the system resulting from the transfer of a proton from the acidic methylene group of the five-membered ring to the basic ionised carboxyl group, is so stabilised by resonance that O-methylation then occurs.

The suggestion that XXXIII exists as a zwitterion can explain the formation of the anhydro salt but is unsatisfactory in that it does not account for the formation of the ester. An alternative explanation is found by analogy with 8-hydroxyquinoline. 8-hydroxyquinoline reacts with diazomethane to give the betaine XLIII. From the study of the ultra-violet absorption spectra of



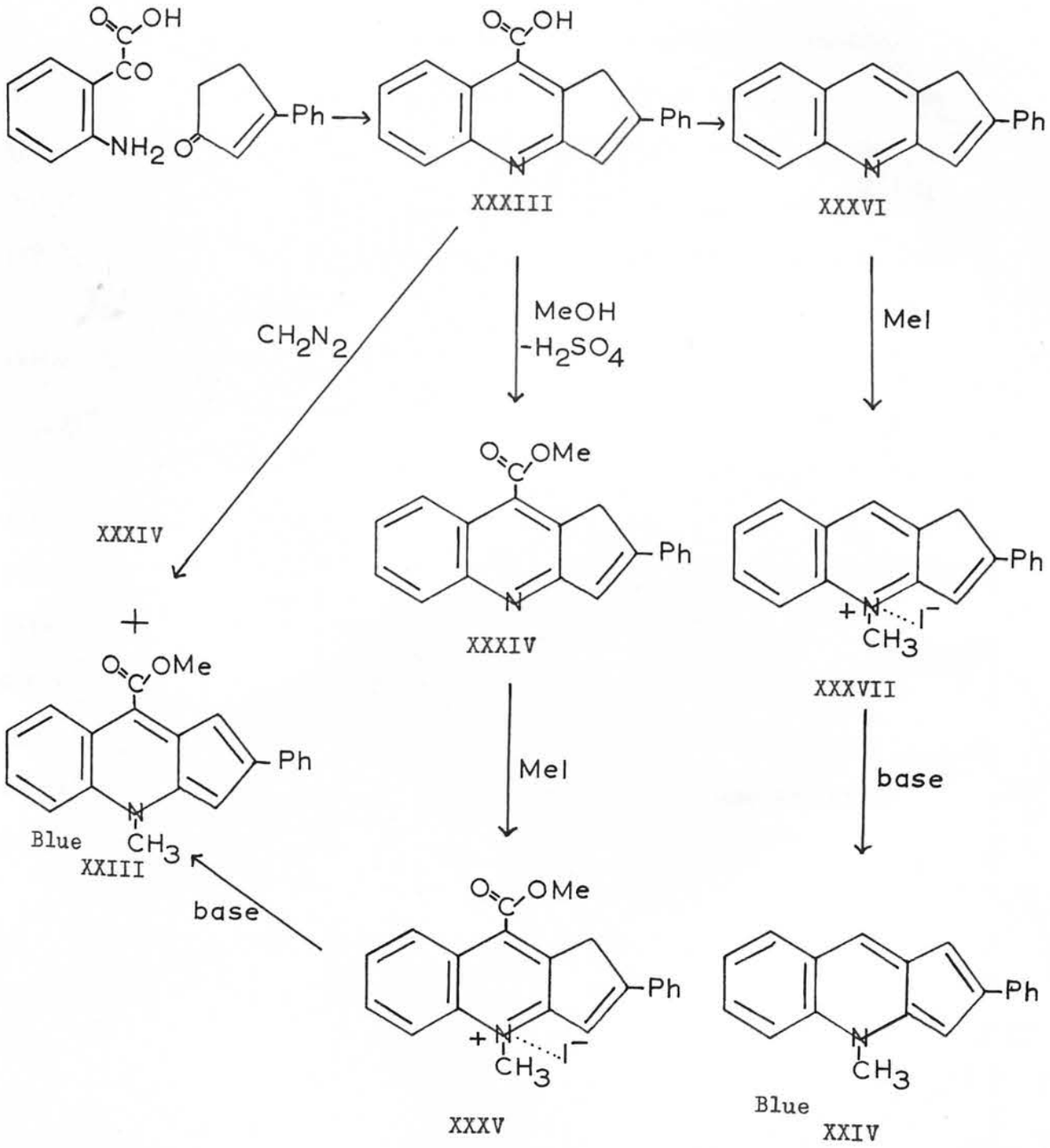
XLIII



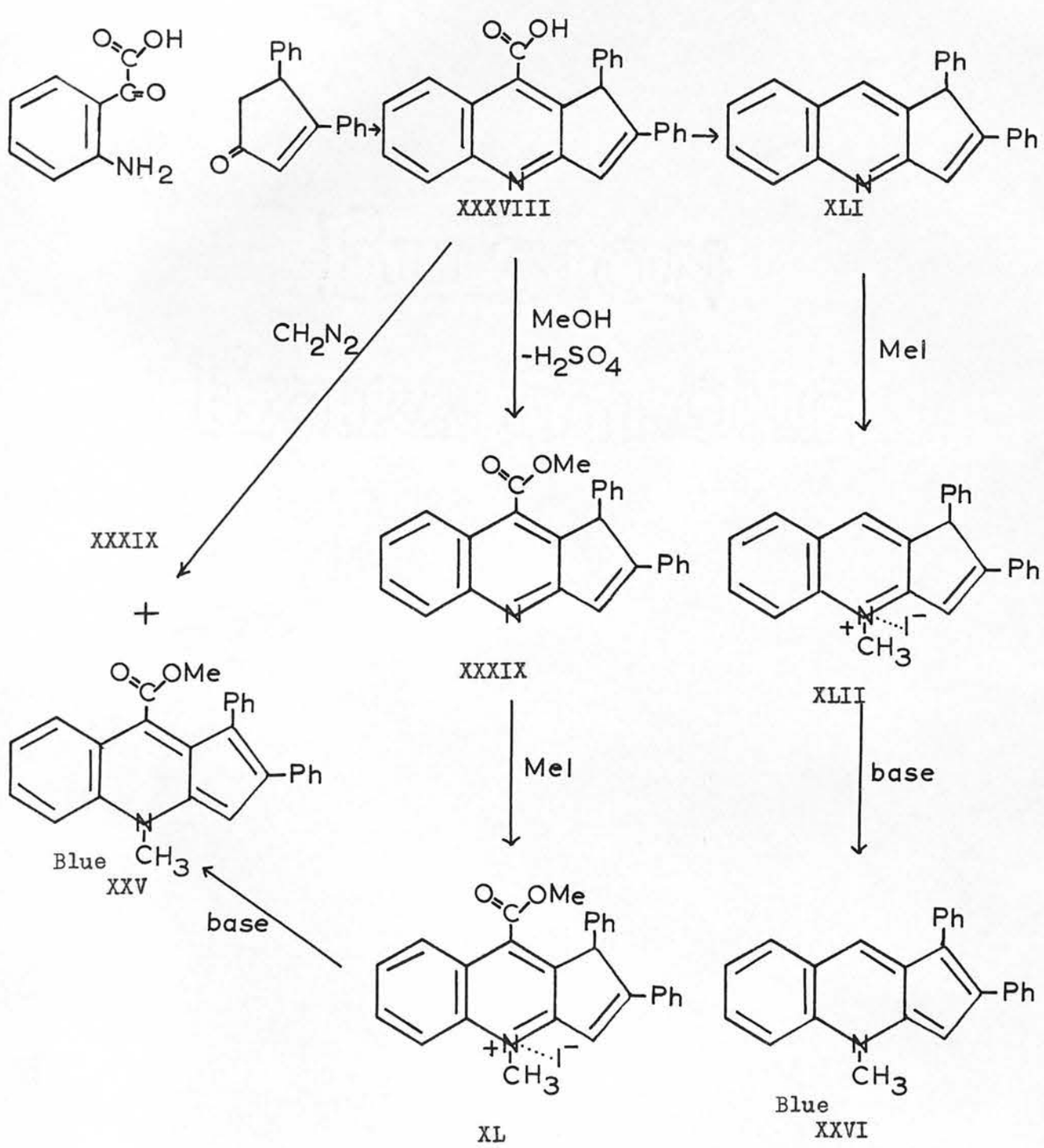
XLIV

8-hydroxyquinoline and its derivatives in acidic, neutral and basic solvents, Philips et al. (J.A.C.S., 1951, 73, 630) conclude that 8-hydroxyquinoline exists as XLIV in neutral solution i.e. that there is intramolecular hydrogen bonding between the oxygen and nitrogen atoms. If intermolecular hydrogen bonding is assumed in the case of XXXIII, methylation could occur at either

REACTION SCHEME III



REACTION SCHEME IV

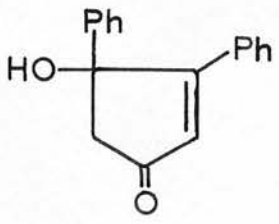


the nitrogen or oxygen atoms in which case, betaine or ester formation would occur respectively giving two products. This appears to be the more likely explanation.

The same ester, XXXIV was obtained by the action of methanol/ sulphuric acid on XXXIII. Methylation with methyl iodide in benzene gave the methoidide, XXXV which, on treatment with sodium carbonate solution gave a blue betaine whose T.N.B. complex had identical melting point with that obtained from the diazomethane reaction, XXIII.

With this success, a second Pfitzinger synthesis was achieved employing 3:4-diphenylcyclopent-2:3-en-1-one as starting material.

It had been generally accepted until 1955 that this compound had the double bond in the 3:4-position although chemical evidence was obtained to the contrary (Burton and Shoppee, J.C.S., 1939, 567, 1408). Allen and Van Allen (J.A.C.S., 1955, 77, 2316) have shown by ultra-violet spectroscopy that the compound is an α-β-unsaturated ketone. The ultra-violet spectrum of diphenyl-cyclopentenone was measured again in ethanol together with anhydroacetone benzil XLV, (its precursor)and their semicarbazone derivatives (Figs. 1 and 2).



XLV

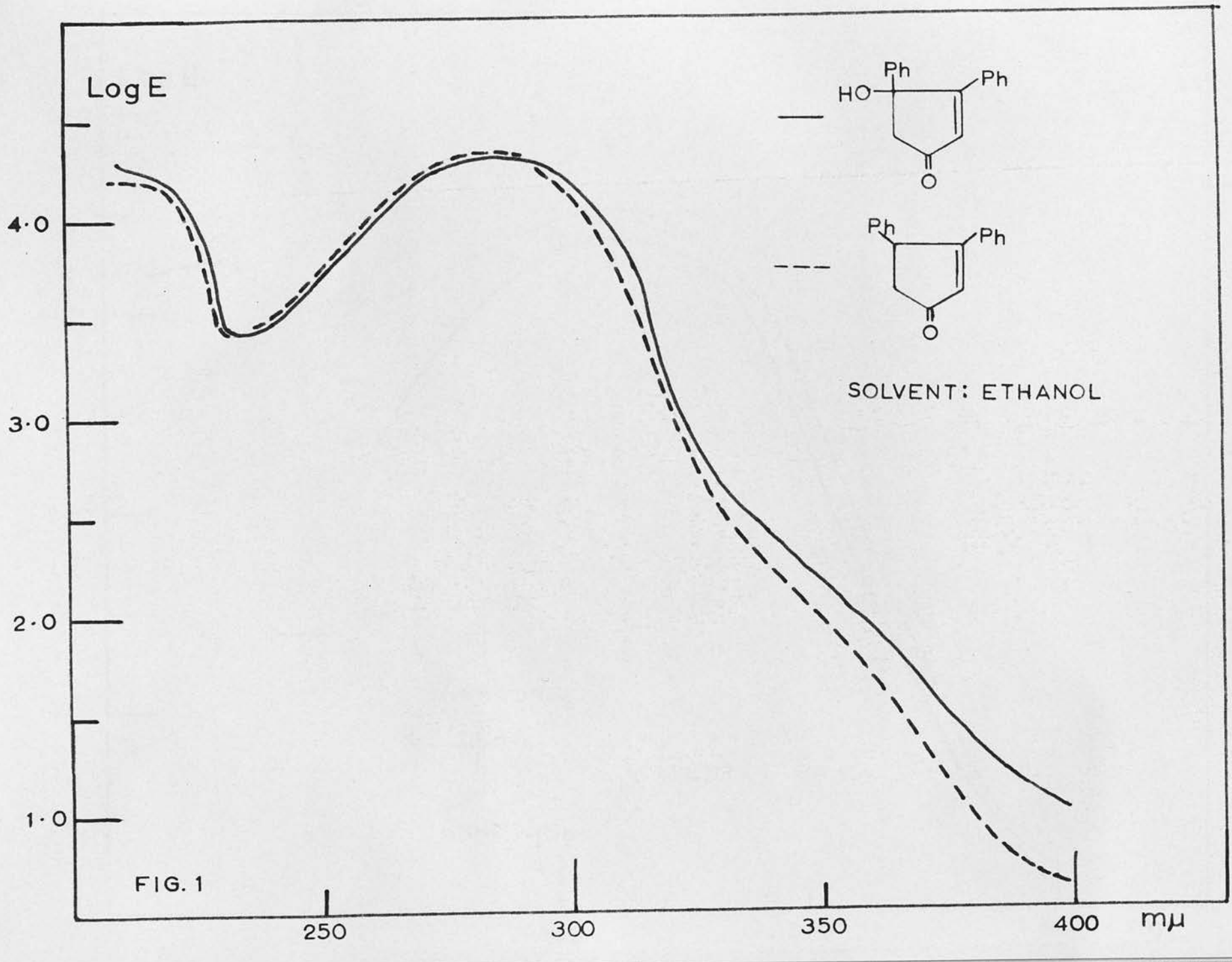

Log E
4·0
3·0
2·0
1·0
250
300
350
400
mμ
HO
Ph
Ph
O
Ph
Ph
O
SOLVENT: ETHANOL

FIG. 1

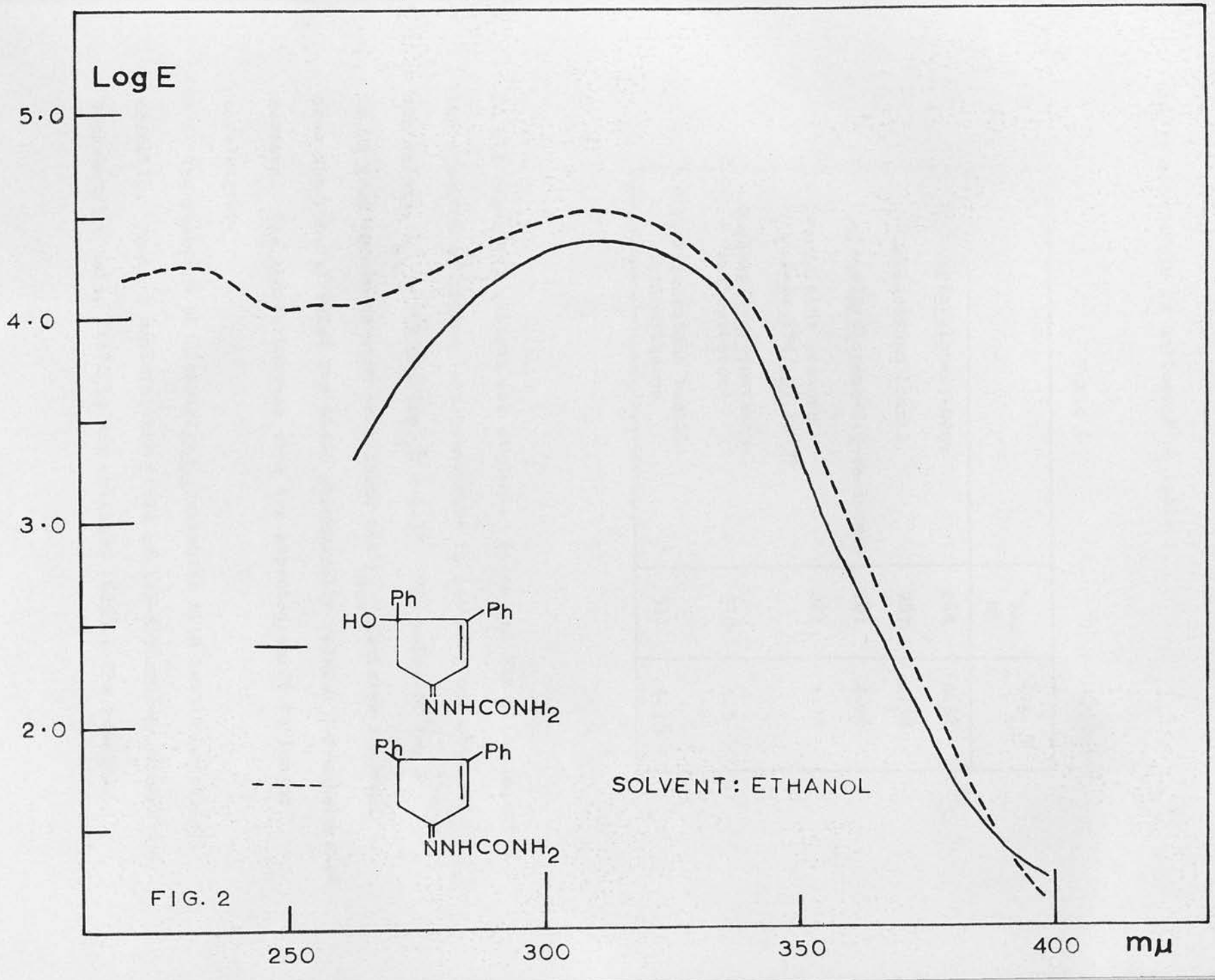

Log E
5·0
4·0
3·0
2·0
HO
Ph
Ph
NNHCONH2
Ph
Ph
NNHCONH2
SOLVENT: ETHANOL
250
300
350
400
mμ

FIG. 2

The relevant data is collected in table I.

Table I

	λ_{max} mμ	$\log_{10}E$
Diphenylcyclopentenone	284	4.32
Anhydroacetone benzil	287	4.30
3-phenylcyclopent-2:3-en-1-one	281	4.36
Benzylidine acetone (J.A.C.S.,1947,69,1985)	286	4.37
Diphenylcyclopentenone semicarbazone	310	4.5
Anhydroacetone benzil semicarbazone	311	4.35

In all cases the solvent was ethanol. Allen and Van Allen measured the spectrum of diphenylcyclopentenone in methanol and obtained the values, λ_{max} = 274 mμ, $\log_{10}E$ = 4.32. The value of log E is in good agreement with that found but λ_{max} deviates somewhat from the general value for these structurally related α-β-unsaturated ketones. The semicarbazones show the expected shift to longer wavelengths.

The reaction of diphenylcyclopentenone with isatin proceeded normally. Again a satisfactory yield of 1:2-diphenyl-β-quinindine-9-carboxylic acid, XXXVIII, was obtained (62%). The reaction

scheme IV was carried out.(p.36).

In the reaction of the acid with diazomethane both ester, XXXIX, and the blue anhydro salt, XXV, were obtained. Methylation of the acid with methanol was found to require a much higher concentration of sulphuric acid than did that of XXXIII. Methylation of the ester with methyl iodide gave the methoiodide, XL, which yielded the same blue betaine as the diazomethane reaction.

The Pfitzinger reaction is generally carried out with a ratio of isatin to ketone of 1:3 moles. The apparent reason is to ensure that all the isatin employed is converted to the quinoline derivative. Isatin would otherwise be precipitated on acidification with acetic acid. Borsche, (Ann., 1910, 377, 120), in the synthesis of 2:3-dihydro-β-quinindine-9-carboxylic acid, employed three moles of cyclopentanone to one mole of isatin. This was found to be a wasteful excess and comparable yields were obtained when only two moles of cyclopentanone were used. Experimental difficulties are introduced when such a large excess of solid ketones are used. Solids and tars separate from the reaction mixture and better and cleaner results are obtained when stoichometric quantities are employed together with a greater proportion of ethanol to maintain solution of the ketone.

The decarboxylation of XXXIII and XXXVIII proved difficult. A standard procedure consists of heating the acid in quinoline in the presence of copper bronze. This introduces difficulties in the isolation of the product. 2-Methyl naphthalene as solvent

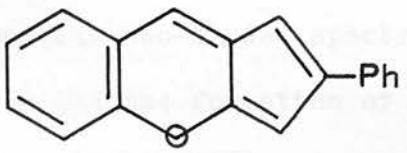
proved unsuccessful. Buu-Hoï and Royer (J.C.S., 1948, 106) found that they could decarboxylate quinaldine-4-carboxylic acid by dry distillation at atmospheric or reduced pressure. They obtained however two products, quinaldine and 4-hydroxyquinaldine. This method also failed. The method which finally gave the desired product was that of dry distillation of the acid with soda-lime under reduced pressure. XLI sublimed into an ice-cooled U-tube whereas XXXVI collected at the top of the decarboxylating vessel. Both were obtained in poor yield.

The 1:2-diphenyl-β-quinindine, XLI, (Scheme IV) had very different properties to the parent acid. Solutions of XLI rapidly turned brown and the acid or ester groupings appear to stabilise the system. XLI showed good solubility in most organic solvents and could be recrystallised from ethanol. It gave a yellow picrate and hydrochloride. Solutions in dilute acid had an intense blue fluorescence. Methylation with methyl iodide gave a yellow methoiodide, XLII, which yielded a blue anhydro salt, XXVI, on treatment with sodium carbonate solution. XXXVI was not obtained pure but converted directly to the methoiodide XXXVII. Treatment with sodium carbonate gave a reddish-blue betaine, XXIV, characterised as its T.N.B. complex.

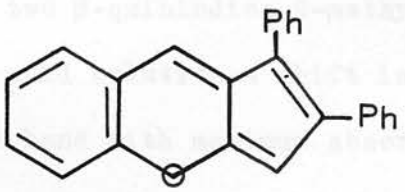
Borsche (loc. cit.) prepared 2:3-dihydro-β-quinindine by the condensation of o-aminobenzaldehyde with cyclopentanone. Neither from the condensation of o-aminobenzaldehyde with 3-phenylcyclopentenone nor with 3:4-diphenycyclopentenone could the desired products be

isolated, although the conditions were those used by Borsche.

It is relevant at this point to deviate from the quinindines to cyclopentapyran derivatives mentioned at the end of the introduction and discussion. Boyd (Chem. and Ind., 1957, 1244) has synthesised XLVI.



XLVI



XLVII

3:4-diphenylcyclopentenone did not condense with salicylaldehyde in ethanolic sodium hydroxide as does 3-phenylcyclopentenone. Condensation was effected by boiling an ethanolic solution of the reactants in the presence of piperidine acetate. Cyclisation to the pyran XLVII proceeded smoothly by heating the salicylidine derivative in acetic acid-hydrochloric acid solution. The nitrogen analogues of XLVI and XLVII have been prepared and a comparison of the ultra-violet and visible absorption spectra is of interest. A strict comparison of the spectra in acid solution is not possible due to the lack of basicity of these compounds although both give yellow, fluorescent pyrillium salts thereby removing the band in the visible part of the spectrum.

The relevant spectra are given in figures 3-13. The solvent in all cases was ethanol and for spectra in acid solution, three drops of analar concentrated hydrochloric acid were added to the

ethanolic solution. In this way, there is no appreciable change in concentration of the substance under investigation.

The positions and log E values of the absorption maxima of the compounds which have been described are collected in Table II.

The salient features arising from these spectra are as follows:

(1) 2-styryl quinoline and the two β-quinindine-9-methyl esters show similar two-banded spectra. In acid solution a shift is observed and the formation of a third band with maximum absorption at 257 mμ (Figs. 4-6).

(2) The anhydro salts generally show broad absorption in the visible and two bands in the ultra-violet (Figs. 7-11). It is noticable that only in the case of 3-phenyl-β-quinindine (Fig. 8) is there any fine structure in the region 370-400 mμ. In the related compounds, this appears as a single band with maximum absorption at 370-390 mμ. In acid solution, the broad band in the visible region disappears and a slight bathochromic shift occurs in the ultra-violet. The anhydro salts in acid solution have the same spectrum as the parent esters in acid solution i.e. λ_{max} at c.400 and 300 mμ. This is to be expected since salts of the esters give the same system as their anhydro salts in acid solution. There is one exception (Fig. 12). 1:2-Diphenyl-β-quinindine shows an abnormal spectrum in acid solution. This might be attributed to a mixture of isomers in the parent compound.

Table II

	Solvent: Ethanol			Solvent: Ethanol/HCl	
	λ_{max} mμ	$\log_{10}E$		λ_{max} mμ	$\log_{10}E$
Ethyl 2-styrylcinchonate	348 292	4.08 4.32		377 290 257	4.06 4.13 4.21
Methyl 2-phenyl-β-quinindine-9-carboxylate	362 293	4.37 4.37		397 299 257	4.49 4.17 3.38
Methyl 1:2-diphenyl-β-quinindine-9-carboxylate	347 329 292	4.34 4.32 4.24		400 299 256	4.55 4.13 4.08
Anhydro-2-phenyl-N-methyl-β-quinindine -9-carbomethoxylate hydroxide.T.N.B.	574 379 297 232	3.17 4.32 4.51 4.45		404 300	4.49 4.21
Anhydro-1:2-diphenyl-N-methyl-β-quinindine -9-carbomethoxylate hydroxide.T.N.B.	574 396 285	3.06 4.41 4.59		403 300	4.59 4.19
Anhydro-2-phenyl-N-methyl-β-quinindine hydroxide.T.N.B.	532 390 370 279	3.01 4.20 4.30 4.47		393 377 292	4.42 4.43 4.14
Anhydro-1:2-diphenyl-N-methyl-β-quinindine hydroxide.T.N.B.	554 372 285	3.28 4.33 4.58		390 326 293	4.34 4.12 4.31
2-phenylbenzocyclopentapyran	470 387 368 256	2.71 4.37 4.56 4.52			
1:2-diphenylbenzocyclopentapyran	512 366 265	2.92 4.47 4.54			

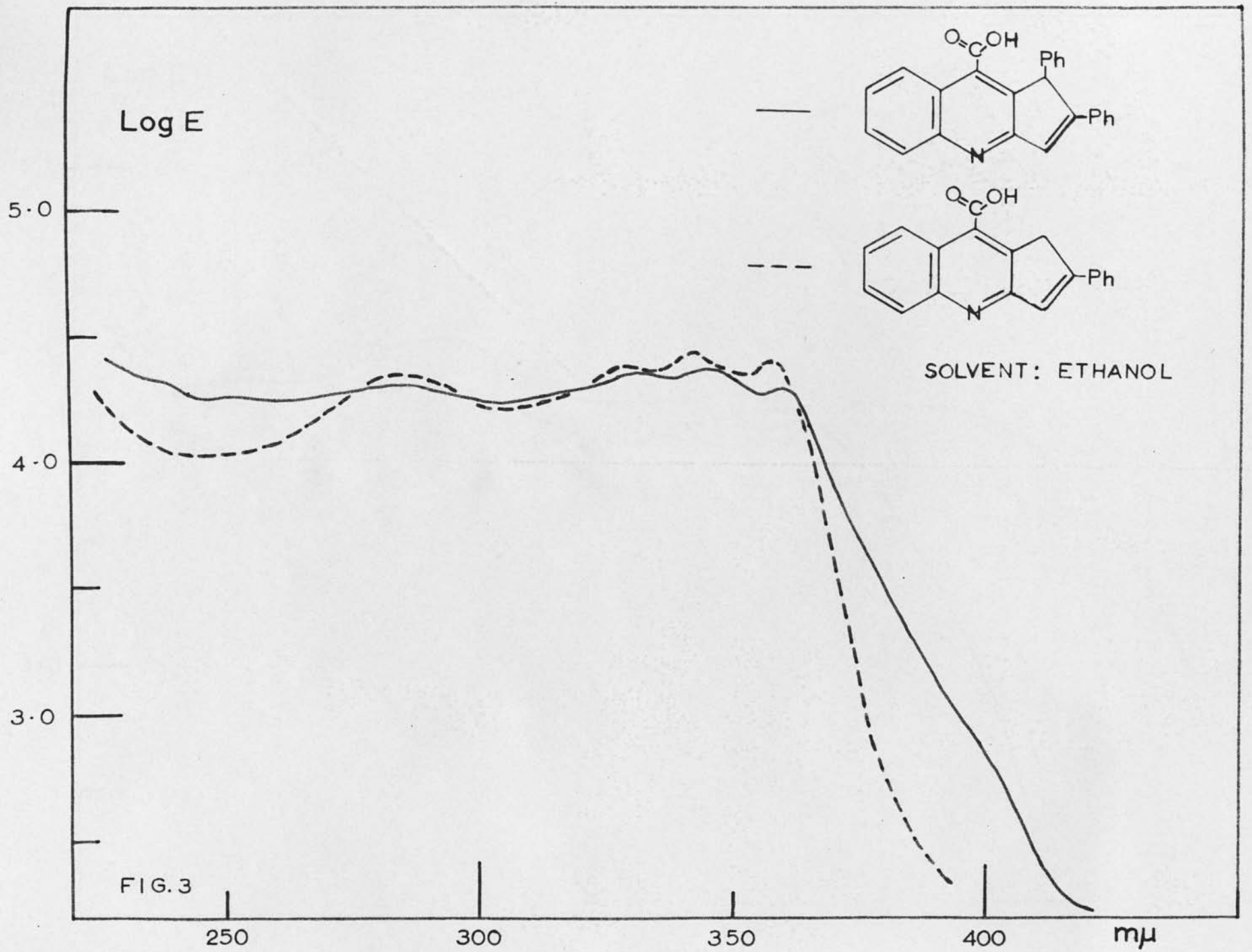

Log E
5·0
4·0
3·0
250
300
350
400
mμ
O=C-OH
Ph
Ph
N
O=C-OH
Ph
N
SOLVENT: ETHANOL

FIG. 3

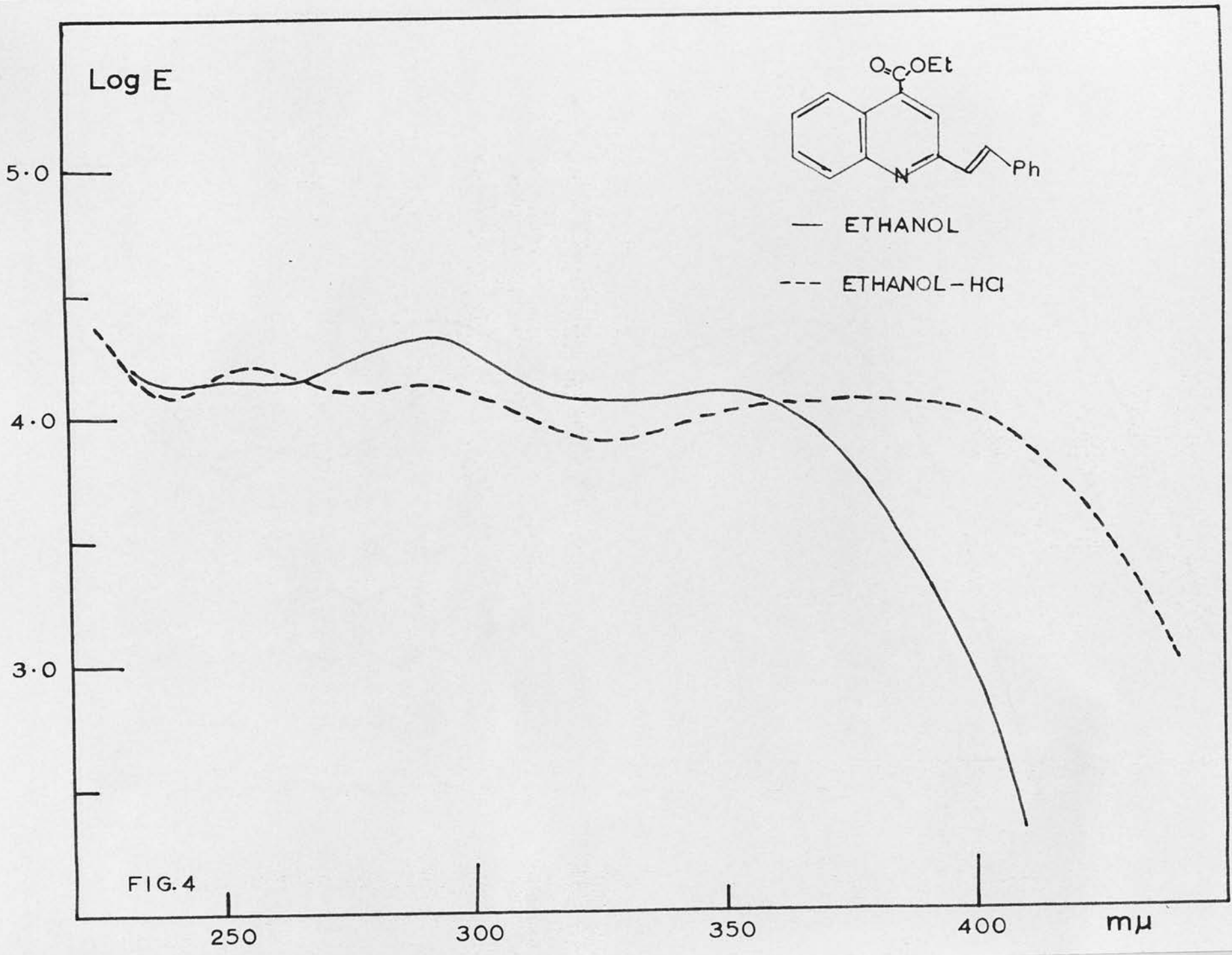


FIG. 4

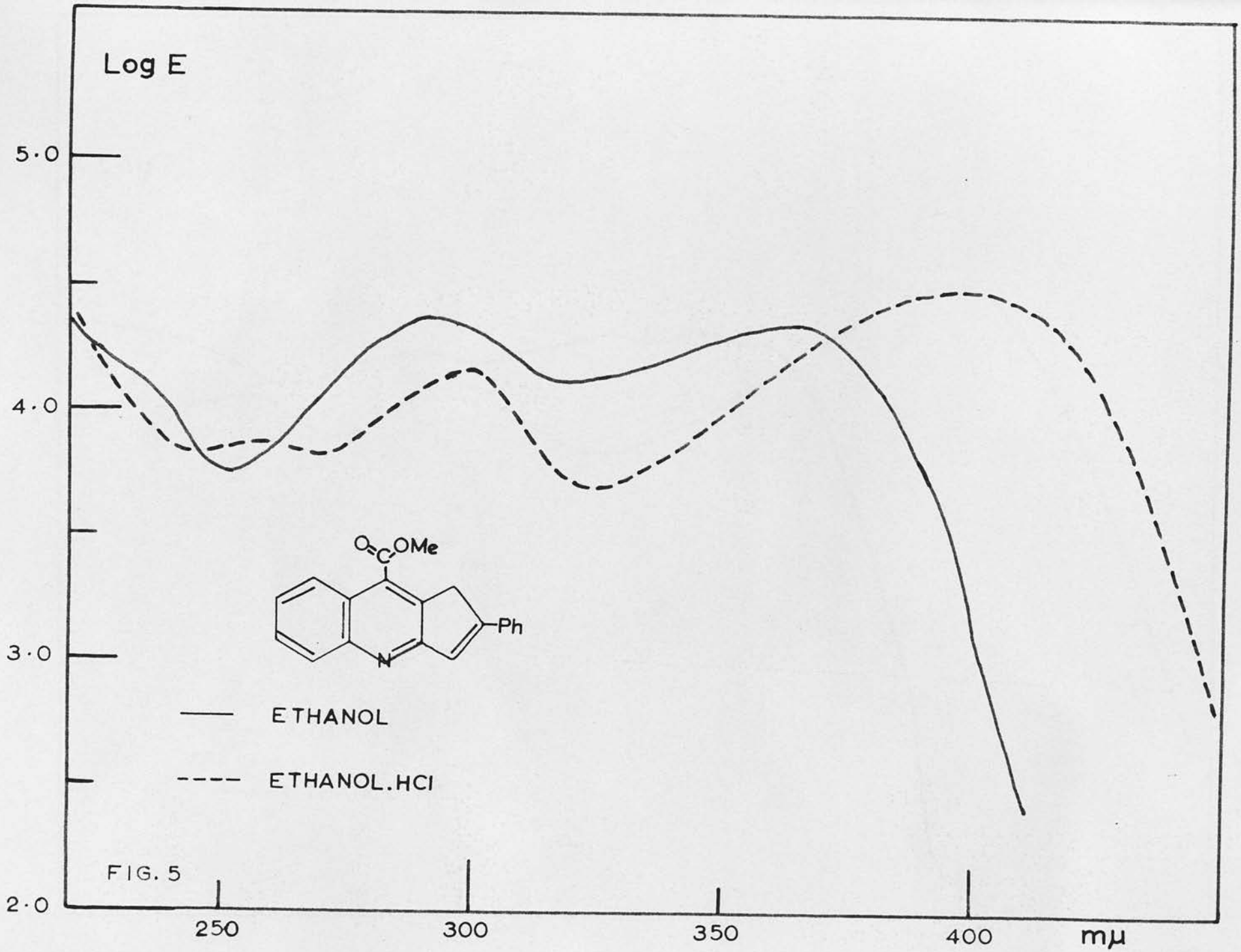

Log E
5·0
4·0
3·0
2·0
250
300
350
400
mμ
O=C-OMe
Ph
N
ETHANOL
ETHANOL.HCl

FIG. 5

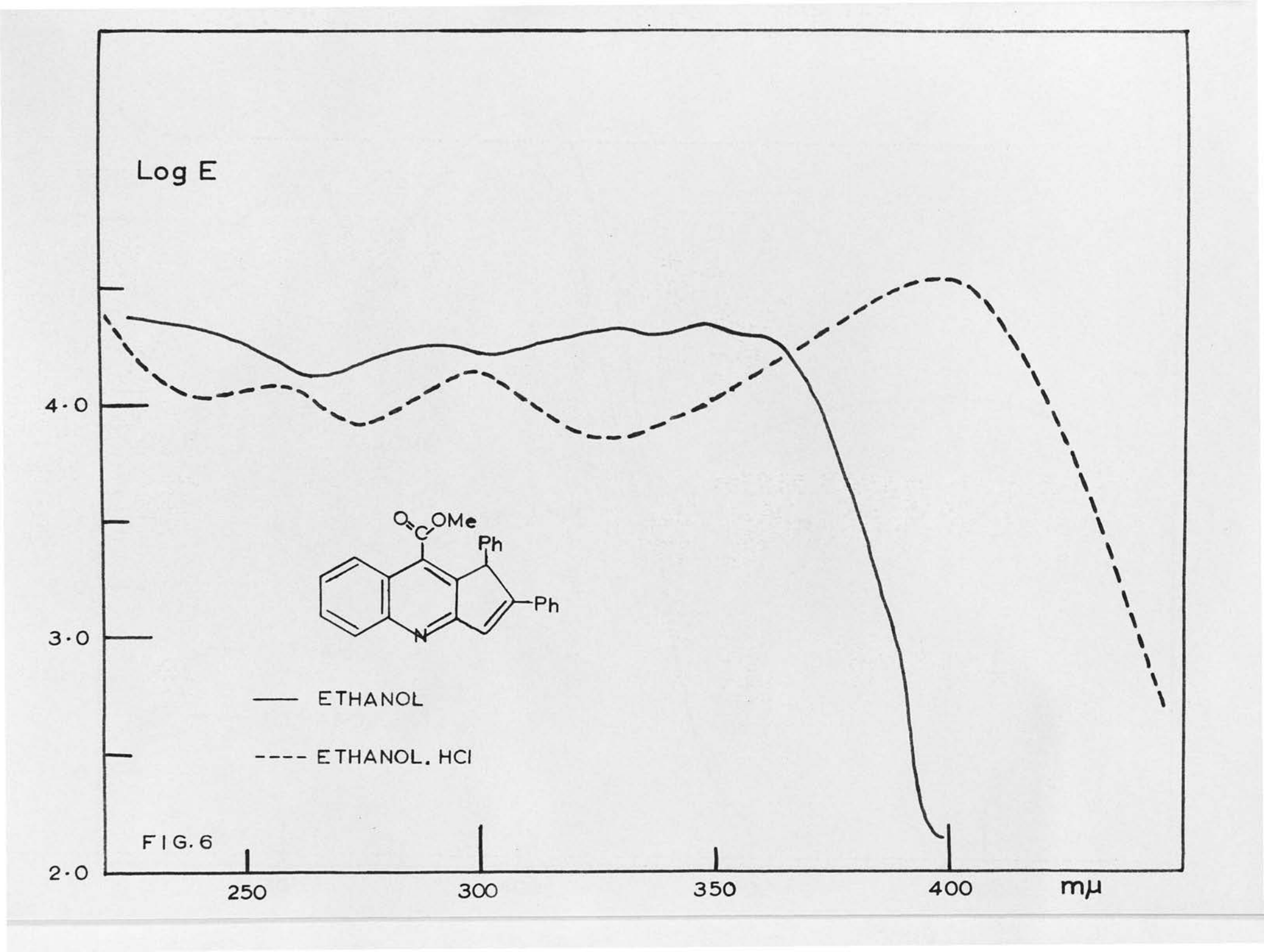

Log E
4·0
3·0
2·0
250
300
350
400
mμ
O=C
OMe
Ph
Ph
N
ETHANOL
ETHANOL. HCl

FIG. 6

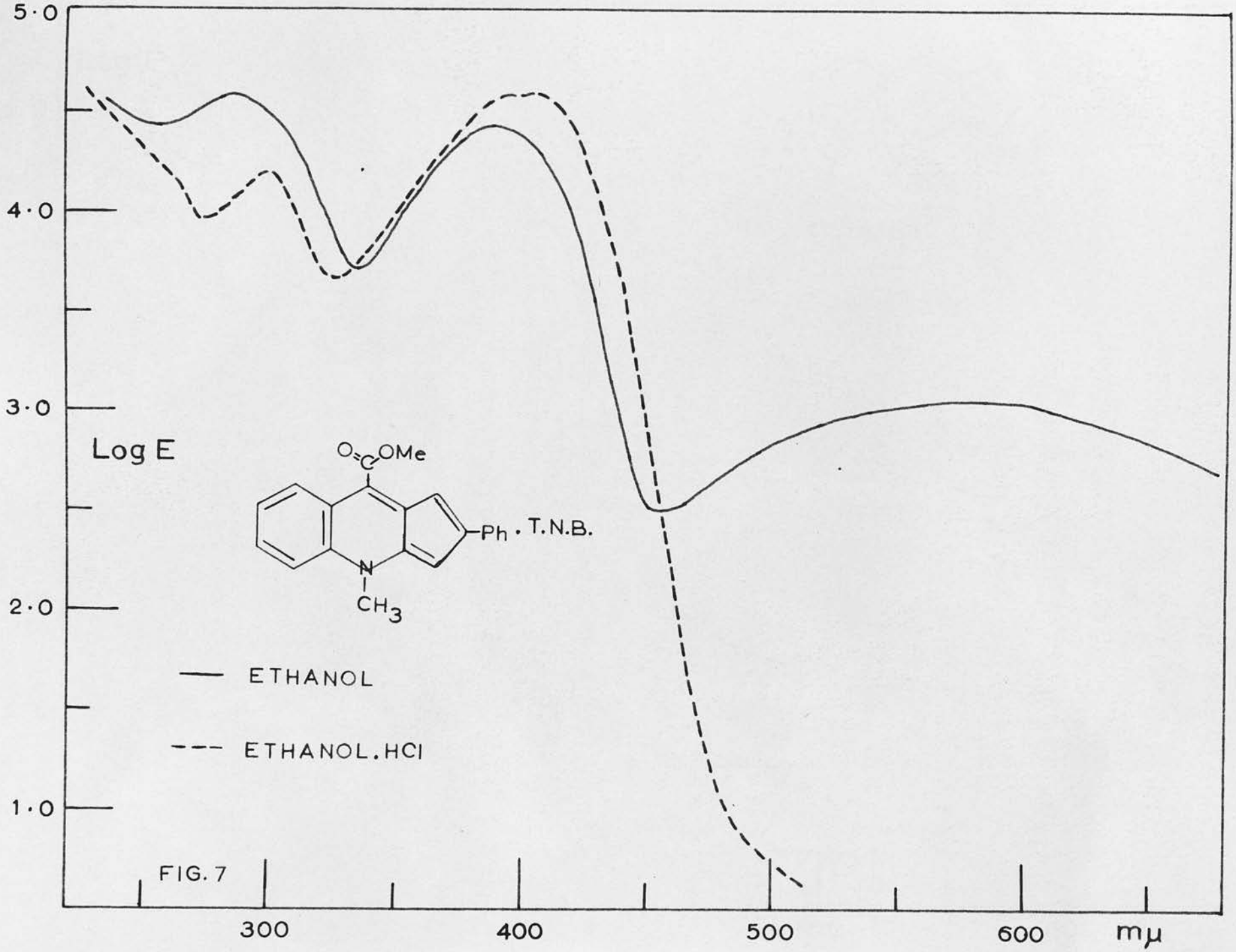

5·0
4·0
3·0
2·0
1·0
Log E
O=C OMe
Ph . T.N.B.
N
CH3
ETHANOL
ETHANOL.HCl
300
400
500
600
mμ

FIG. 7

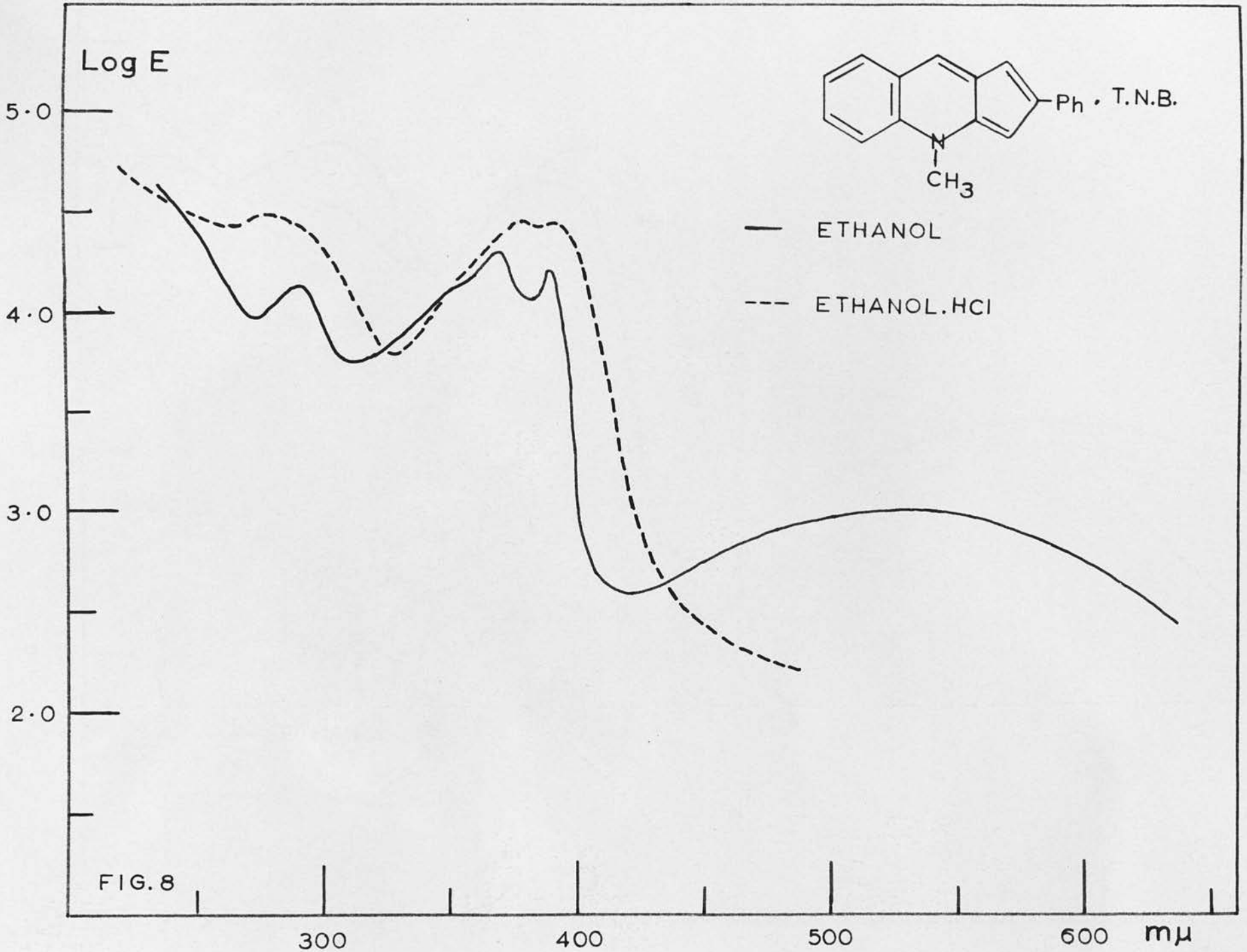

Log E
5·0
4·0
3·0
2·0
Ph
T.N.B.
N
CH3
ETHANOL
ETHANOL.HCl
300
400
500
600
mμ

FIG. 8

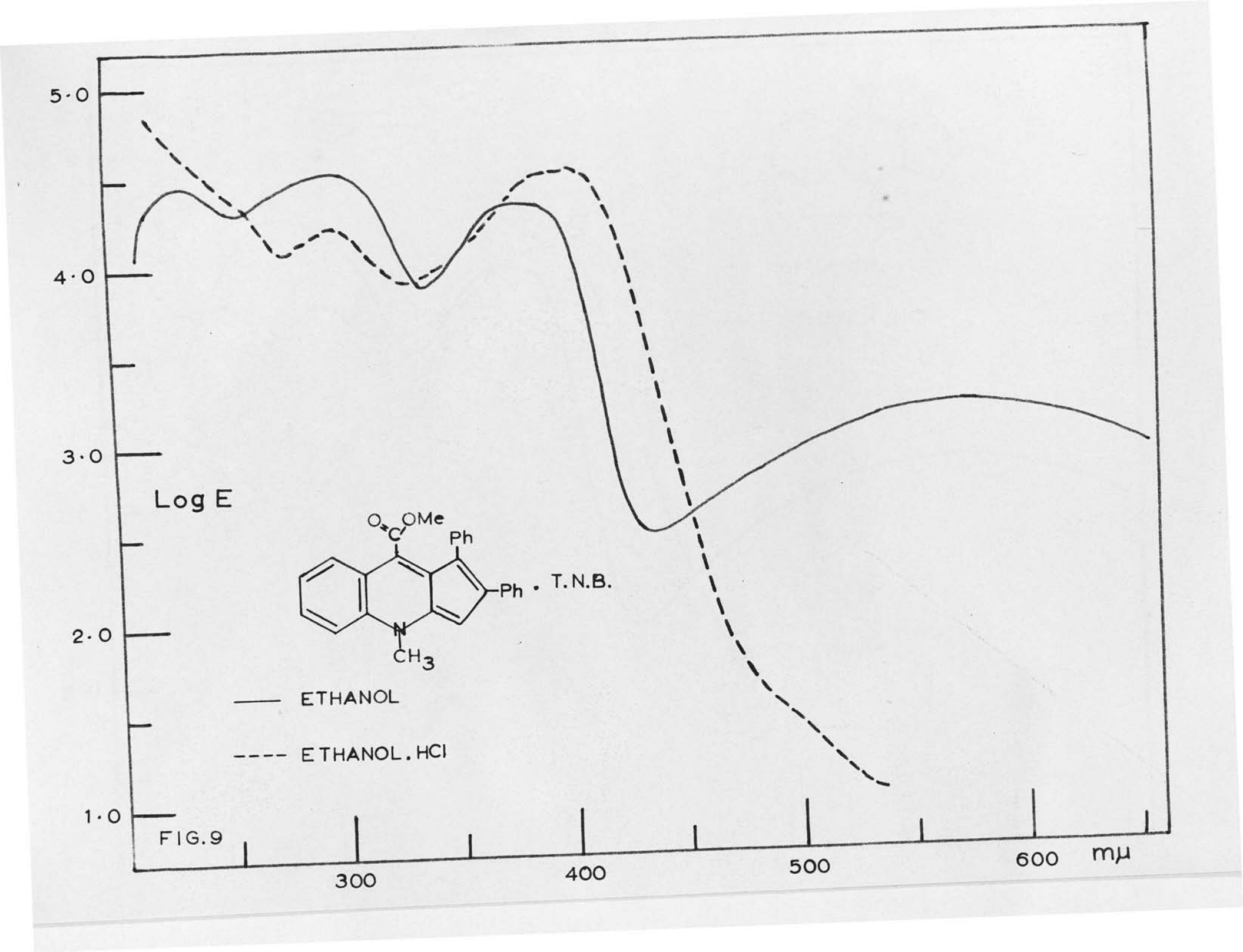

5·0
4·0
3·0
2·0
1·0
Log E
O
C
OMe
Ph
Ph
N
CH3
T.N.B.
ETHANOL
ETHANOL.HCl
300
400
500
600
mμ

FIG.9

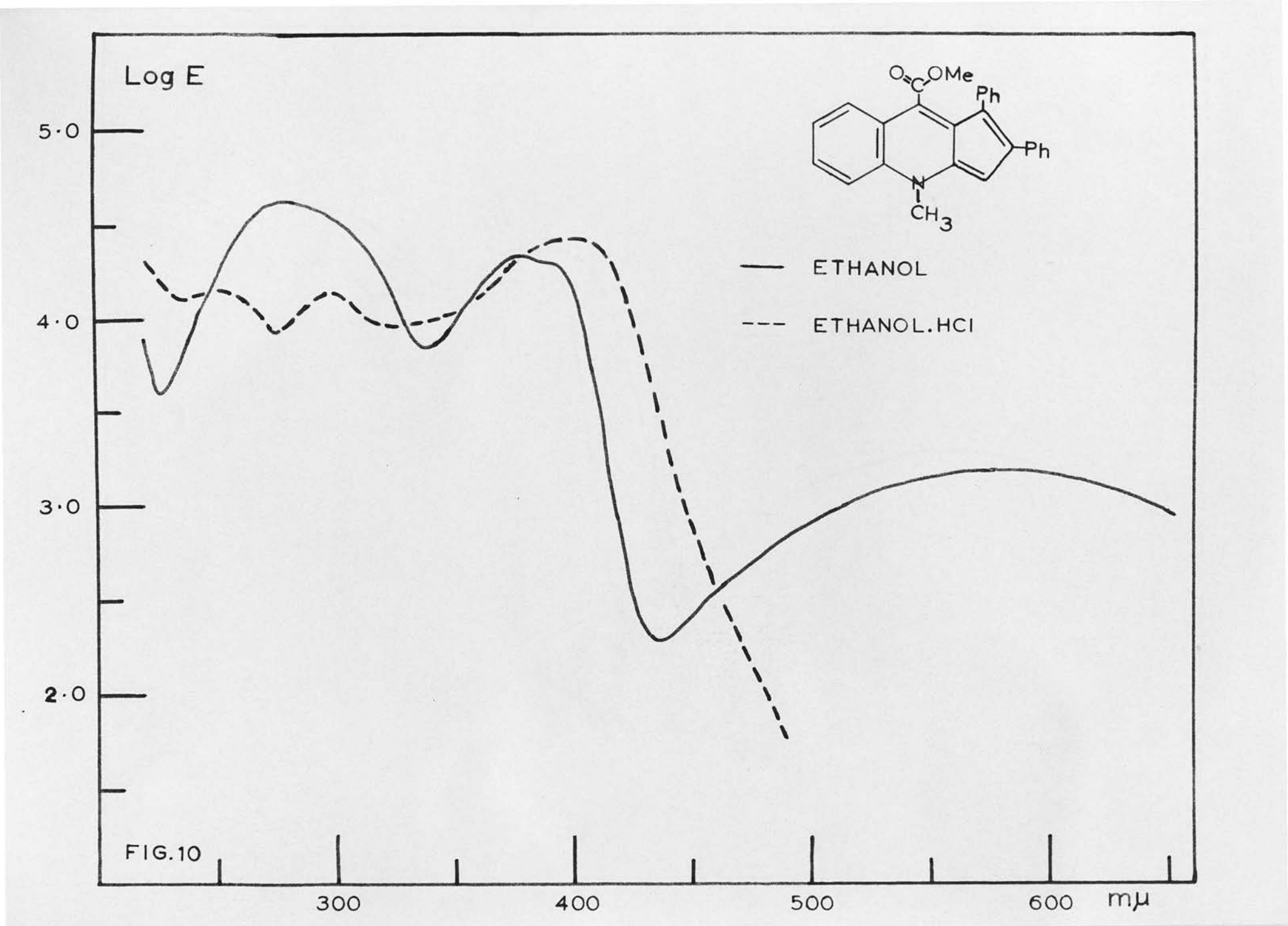

Log E
5·0
4·0
3·0
2·0
O=C OMe
Ph
Ph
N
CH3
ETHANOL
ETHANOL.HCl
300
400
500
600
mμ

FIG.10

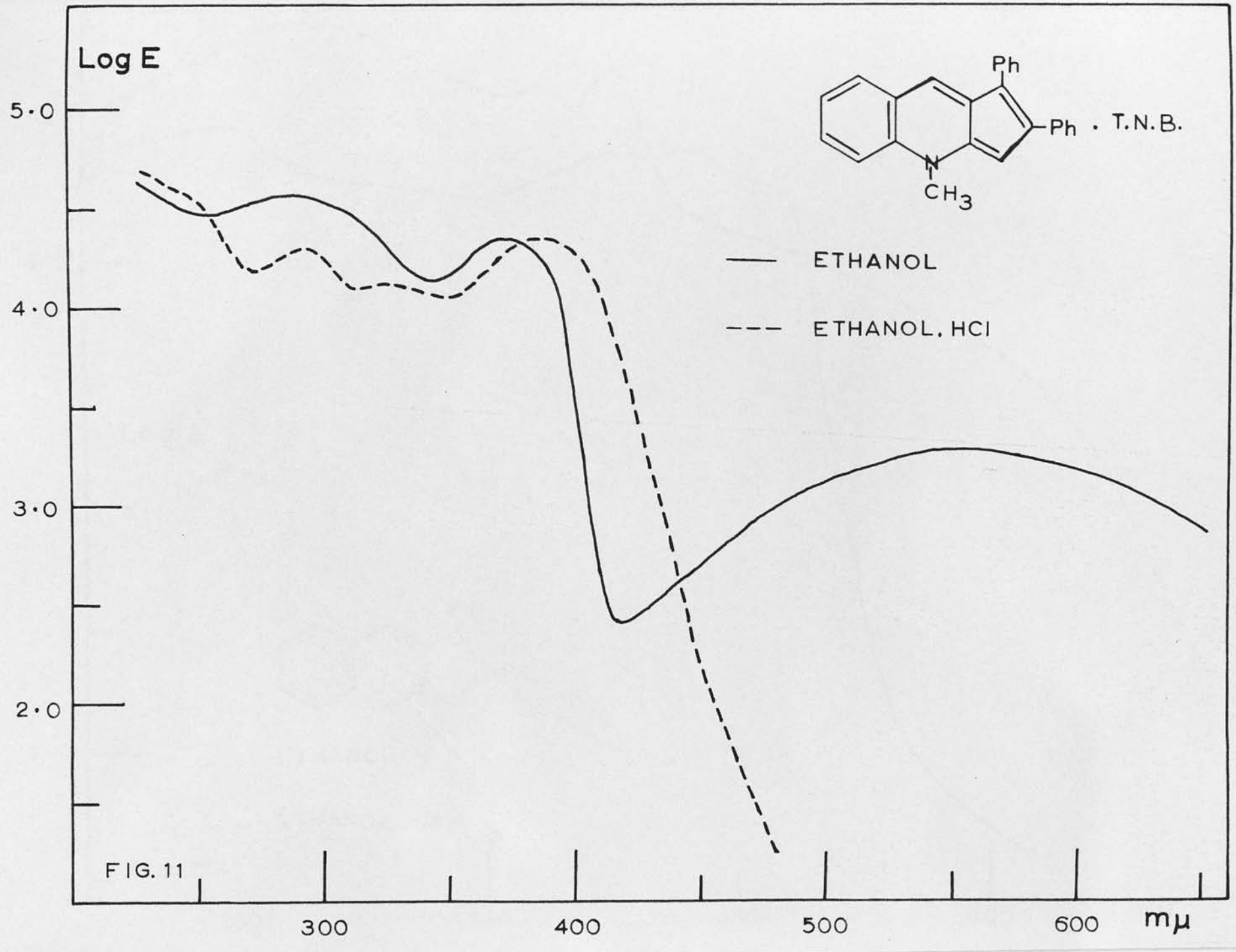

Log E
5·0
4·0
3·0
2·0
Ph
Ph
N
CH3
· T.N.B.
ETHANOL
ETHANOL. HCl
300
400
500
600
mμ

FIG. 11

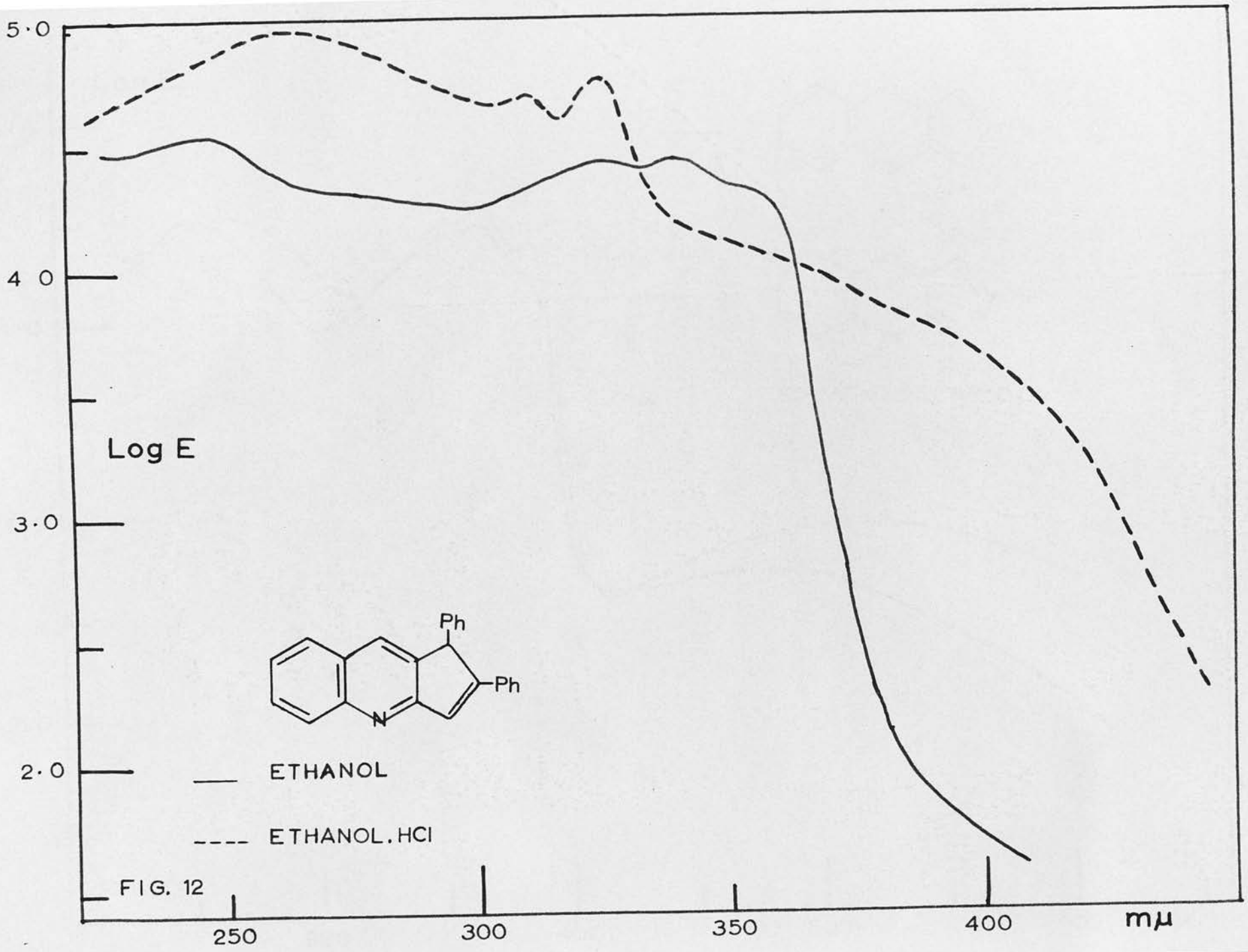


FIG. 12

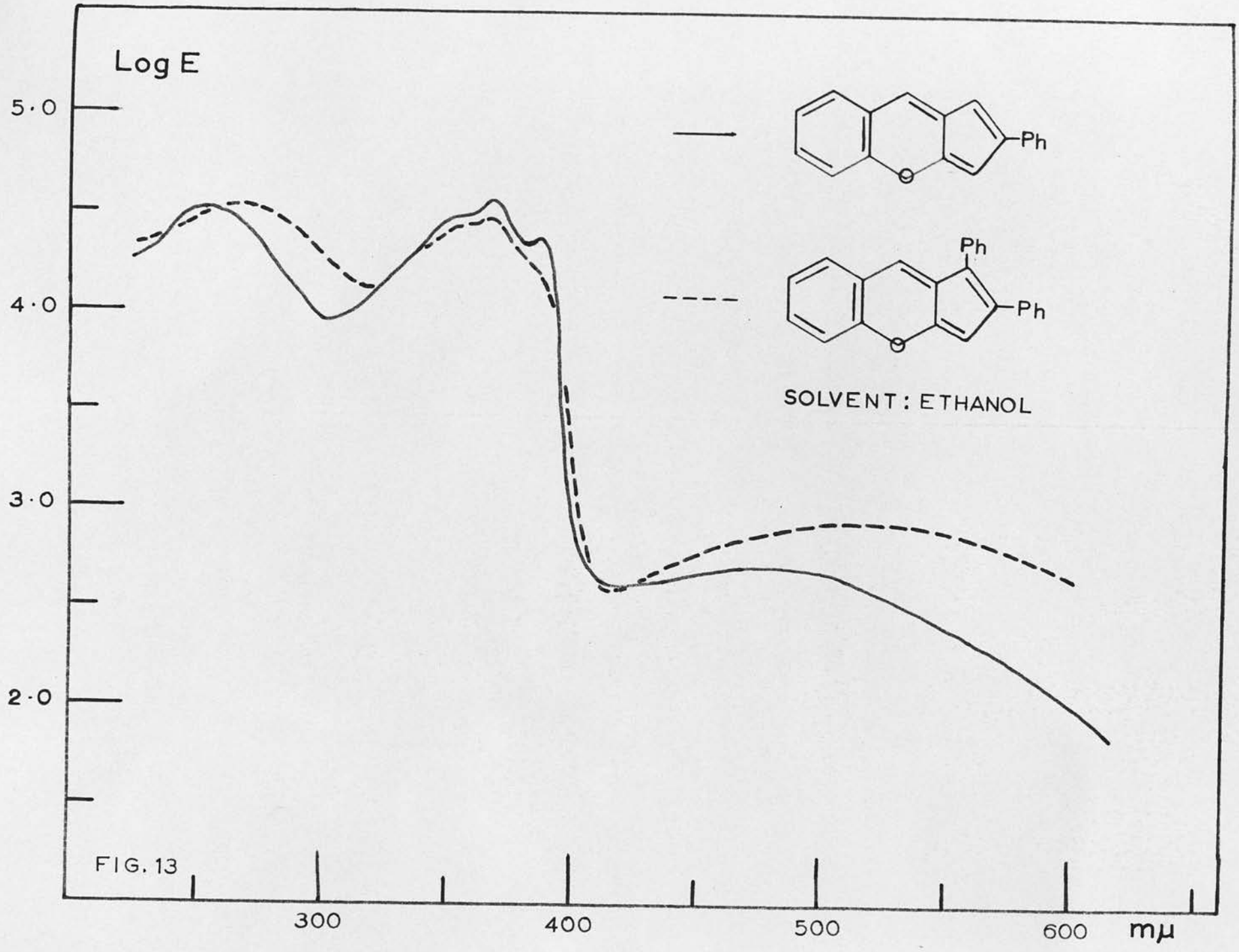


FIG. 13

(3) The maxima in the visible spectrum of the anhydro salts show a regular displacement except in the case of 2-phenyl-β-quinindine-9-ester and the 1:2-diphenyl ester, (Figs. 7 and 9), which show identical maxima. This is unexpected but can be explained by a "crowding" effect. The phenyl group in position 1 may not be able to assume a planar configuration with respect to the five-membered ring due to the proximity of the 9-carbomethoxy and 3-phenyl groups. If this is so, then the phenyl group will be unable to conjugate with the π -electron system of the quinindine nucleus and will not affect the absorption in the visible region of the spectrum. This theory is substantiated by a consideration of the spectra of these anhydro salts as a whole. One structure is common to all the anhydro salts, i.e., 2-phenyl-β-quinindine. If this is considered as the starting point, then the shifts in the maxima in the visible spectra of the anhydro salts can be tabulated as follows:

1:2-diphenyl-β-quinindine	λ_{max} 554mμ
2-phenyl-β-quinindine	λ_{max} 532mμ
Shift due to the 1-phenyl group	+22mμ
2-phenyl-β-quinindine-9-carboxylate	λ_{max} 574mμ
2-phenyl-β-quinindine	λ_{max} 532mμ
Shift due to the 9-carbomethoxy group	+42mμ
1:2-diphenyl-β-quinindine-9-carboxylate	λ_{max} 574mμ
1:2-diphenyl-β-quinindine	λ_{max} 554mμ
Shift due to the 9-carbomethoxy group	+20mμ

As can be seen, the two displacements found for the 9-carbomethoxy group are not identical. The 1-phenyl group is shown to cause a bathochromic shift of 22 mμ. 1:2-diphenyl-β-quinindine-9-carboxylate should then have its λ_{max} at 594 mμ if the phenyl group in the 1-position were having its expected effect. If this were so, then the shift due to the 9-carbomethoxy group in the diphenyl compound would be 596-554 = + 42 mμ - identical to that found in the monophenyl series. The conclusion is that this phenyl group is sterically hindered and is thus prevented from conjugating with the quinindine nucleus.

(4) The shifts observed in the visible spectra of the anhydro salts is in agreement with that found in the azulenes. Alkyl groups (electron donating) in positions 1,3,5 or 7 cause a bathochromic displacement whereas alkyl groups in positions 2,4,6 and 8 cause a hypsochromic displacement from that of azulene itself. Electron attracting groups e.g., carbomethoxy group have the opposite and larger effect. Position 9 in β-quinindine can be considered equivalent to positions 4 and 8 of azulene. In the β-quinindine series, the carbomethoxy group also has a much greater effect than the phenyl group.

(5) A direct comparison can be made between the spectra of 1-phenyl-β-quinindine, 1:2-diphenyl-β-quinindine and the two oxygen analogues, 2-phenylbenzocyclopentapyran, XLVI, and 1:2-diphenylbenzocyclopentapyran, XLVII (Figs., 8,10,11 and 13). All show essentially the same three banded spectrum. The band at c. 370 mμ has fine

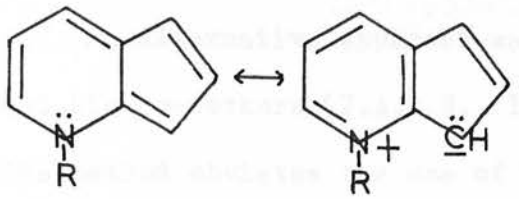
structure only in the 2-phenyl derivatives when each is split up into two peaks. In the oxygen series, the 1:2-diphenyl shows the same bathochromic shift from the 1-phenyl derivative although much larger than that in the nitrogen series (+42 compared with +22 mμ).

These four compounds are identical, at least formally, in all respects except in their heteroatom. The large differences in their λ_{max} (Table III) in the visible part of the absorption spectrum can therefore only be a result of differences in these atoms.

Table III

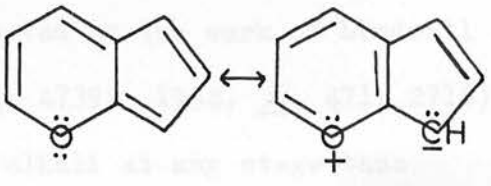
	λ_{max}
2-phenyl-β-quinindine	532
2-phenylbenzocyclopentapyran	470
1:2-diphenyl-β-quinindine	554
1:2-diphenylbenzocyclopentapyran	512

Oxygen is more electronegative than nitrogen. This means that oxygen will show a greater tendency to develop an electron pair than will nitrogen. This electron pair could otherwise be written on the 1 or 3 carbon atoms of the five-membered ring i.e. representing the molecule as a dipolar, betainoid structure. The structure in which the electron pair resides on the heteroatom is purely covalent.



(a) (b)

XLVIII



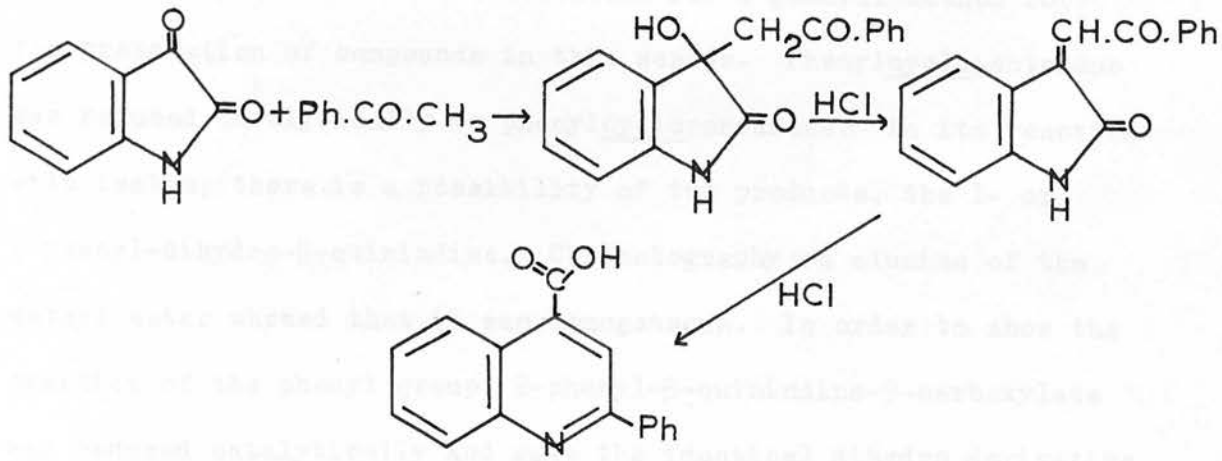
(a) (b)

XLIX

Since increased carbanion contribution is known to increase the depth of colour, only one conclusion can be reached. XLIX (a) must contribute to the actual structure of XLIX to a greater extent relatively than does XLVIII (a) to the actual structure of XLVIII. This is reflected in the basicity of these compounds. Whereas the quinindines are strongly basic, the pyrans are only weakly so since the strongly basic carbanion contributes to a far less extent in the pyran derivatives than in the quinindines.

Having shown that the Pfitzinger reaction is applicable to α-β-unsaturated ketones, an attempt was made at the direct synthesis of β-quinindine by a Pfitzinger reaction with cyclopentenone. This material is now readily available by synthesis from cyclopentadiene according to the method of Alder and Flock (Ber., 1956, 1732). The reaction with isatin was performed under the conditions used by Pfitzinger (J. prakt. Chem., 1897, 56, 283) for the condensation of ethyl acetoacetate. A good yield of a yellow, acidic solid was obtained by conducting the reaction at room temperature. Analysis and subsequent reactions indicated that this was a polymer. The failure of this reaction was thought to be due to the high concentration of alkali and the instability of cyclopentenone.

An alternative approach was suggested by the work of Lindwall and his co-workers (J.A.C.S., 1932, 54, 4739; 1934, 56, 471, 2716). The method obviates the use of strong alkali at any stage thus removing the possibility of self-condensation and polymerisation of cyclopentenone. Isatin is condensed with the ketone in the presence of diethylamine and the reactions carried out as follows:-



Isatin and cyclopentenone were condensed in the presence of piperidine. A small yield of a white solid was obtained. Analysis showed that this product involved two molecules of isatin for each molecule of cyclopentenone. This is rather unusual. There are cases when two molecules of ketone condense with each molecule of isatin e.g., ethyl malonate and ethyl cyanoacetate (Lindwall and Hill, J.A.C.S., 1935, 57, 735; Sumpter, Chem. Revs., 1944, 34, 393). It was therefore of interest to see whether the known 2:3-dihydro-β-quinindine-9-carboxylic acid could be obtained by this route. But again, the anomalous condensation occured between isatin and

cyclopentanone, two molecules of isatin being present for each one of cyclopentanone. The structure of these products was not investigated. This synthesis of substituted cinchonic acids thus appears to have severe limitations.

As 2-phenyl-β-quinindine-9-carboxylic acid was a stable derivative of β-quinindine, attempts were made to synthesise it from its dihydro derivative as a model for a general method for the preparation of compounds in this series. Phenylcyclopentenone was reduced catalytically to phenylcyclopentanone. In its reaction with isatin, there is a possibility of two products, the 1- or 2-phenyl-dihydro-β-quinindine. Chromatography on alumina of the methyl ester showed that it was homogeneous. In order to show the position of the phenyl group, 2-phenyl-β-quinindine-9-carboxylate was reduced catalytically and gave the identical dihydro derivative as obtained by the direct reaction of phenylcyclopentanone with isatin. Buu-Hoï (J.C.S., 1946, 795) found that the analogous reaction occured with 3-methylcyclopentan-1-one and isatin yielding 2-methyldihydro-β-quinindine-9-carboxylic acid.

The most obvious method of introducing a double bond into the five-membered ring, that of bromination-dehydrobromination, was tried. Bromination with N-bromosuccinimide appeared to go normally but the dehydrobromination with either pyridine or methanolic potassium hydroxide produced only a red amorphous solid.

The next step in the attempt to prepare the parent β-quinindine consisted of introducing a functional group other than bromine

into the five-membered ring. The analogous quinoline derivative, quinaldine, has a reactive methyl group due to the electron-attracting properties of the C=N linkage which are increased in the quaternary salt. It readily condenses with benzaldehyde to give 2-styrylquinoline. The quaternary salt condenses even more readily. Similarly, the methylene group α to the ring nitrogen in dihydro-β-quinindine is reactive. Thus it readily undergoes condensation with diethyl oxalate to yield α-keto esters (Borsche and Manteuffel, Ann., 1938, 534, 56). Condensation of the methoiodide with such substances as p-dimethylaminobenzaldehyde in the presence of piperidine or in boiling acetic anhydride proceeds with yields of up to 95% and a series of carbocyanine dyes has also been prepared from the methoiodide. (Petrow, J.C.S., 1945, 18; 1948, 1895). The direct condensation with benzaldehyde is not described.

In quinaldine methoiodide the methyl group is more reactive than quinaldine, and further, the condensation with an aldehyde takes place under the influence of a different reagent (piperidine) from that required by quinaldine (zinc chloride, hydrogen chloride or acetic anhydride). From the reaction of dihydro-β-quinindine methoidide and benzaldehyde in acetic anhydride, no styryl derivative was obtained. Furthermore, the most favourable conditions for the reaction of benzaldehyde and dihydro-β-quinindine was in the presence of piperidine. This does not follow the general rule although Skraup and Böhm (Ber., 1926, 59, 1013) obtained excellent yields of 2-styrylquinoline when using piperidine as the catalyst.

A 64% yield was obtained when a large excess of benzaldehyde was employed and the reaction mixture heated at 150°C, the water formed in the reaction being distilled off as it was produced. The excess benzaldehyde was then removed and the residue triturated with ethanol. The solid can be recrystallised from ethanol in which it has an intense blue fluorescence. 3-benzylidine-dihydro-β-quinindine readily forms a methosulphate on heating in dimethyl-sulphate. Treatment of the methosulphate in ethanol with lithium iodide in ethanol gave the methoiodide.

A standard procedure for the conversion of olefines to aldehydes or ketones is ozonolysis of the double bond followed by hydrolysis. Although innumerable examples can be found in the carbocyclic series, they are few in the heterocyclic series. Lenart (Ber., 1914, 47, 808; Ann., 1915, 410, 95) ozonised α-stilbazole in both carbon tetrachloride and concentrated hydrochloric acid solution. The product isolated was pyridine -2-aldehyde.

Kaslow and Stayner (J.A.C.S., 1945, 67, 1716) made an intensive study of the ozonolysis of benzylidine derivatives of pyridine and quinoline. It was intended to provide an easy route to the otherwise difficultly accessible aldehydes. Benzaldehyde and m-nitrobenzaldehyde were condensed with α and γ picoline, lepidine, quinaldine and 2:4-dimethylquinoline respectively. They obtained the rather surprising result that on ozonolysis all these styryl derivatives gave carboxylic acids in 58-95% yield. The ozonolysis was carried out in glacial or 95% acetic acid.

In an attempt to prepare the aldehydes, the reductive

decomposition of the ozonide with zinc dust and water proved unsuccessful. The aldehydes were not produced by conducting the ozonolysis in anhydrous ethyl acetate or ethyl bromide solution. Kaslow and Stayner noted that towards the end of the ozonolysis, except in the case of α-stilbazole, a finely divided crystalline precipitate separated from the acetic acid solution. This proved to be the acid, not the ozonide.

The ozonolysis of 3-benzylidine-dihydro-β-quinindine was initially conducted in glacial acetic acid. No solid precipitated during the reaction. The ozonide was decomposed with water and zinc dust. Steam distillation of the acid solution gave benzaldehyde, characterised as its 2:4-dinitrophenylhydrazone. The ether extract from the neutral residue yielded a yellow solid. Recrystallisation from ethanol gave pale yellow plates, m.p. 183-184°C., which gave a yellow-orange dinitrophenylhydrazone which decomposed between 275 and 295°C.

Several repetitions of the ozonolysis under these conditions produced none of this yellow solid. Ozonolysis in carbon tetrachloride solution precipitated a solid which was thought to be the ozonide which could not, however, be decomposed cleanly to give a satisfactory yield of the ketone. Anhydrous ethyl acetate was the next solvent to be employed. The first three reactions on the 1gm. scale gave 50% yields of the ketone but successive ozonolyses produced only black tars.

Since anhydrous ethyl acetate did give satisfactory yields of

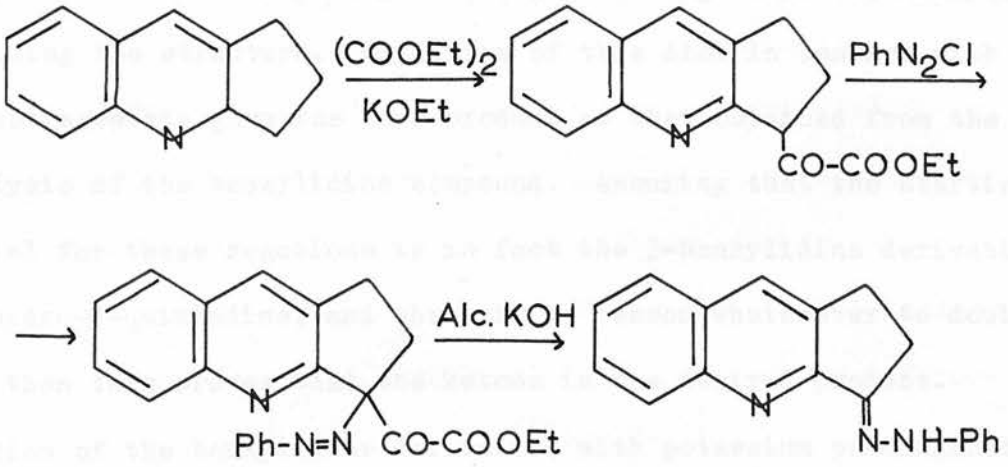
the ketone in the first instance, an examination was made of the failure of succeeding experiments to give the product. It was found that the ketone was most susceptable to oxidation and the ozone concentration had to be rigorously controlled. The ozonolysis was stopped as soon as a slight excess of ozone in the issuing oxygen was indicated by starch-iodide paper. Nitrogen was then bubbled through the solution for 15 minutes. The best method found to decompose the ozonide consisted of passing a stream of hydrogen through the solution in the presence of platinum oxide or palladium charcoal for one hour. Using 2gms. of benzylidine derivative, a yield of 63.5% of ketone was obtained.

Kaslow and Stayner reported that towards the end of ozonisation of most of the benzylidine derivatives in acetic acid, a finely divided crystalline precipitate of the carboxylic acids separated. In the ozonolysis of 3-benzylidine-dihydro-β-quinindine in anhydrous ethyl acetate, the same phenomena was observed. Removal of a sample proved it to be not the ozonide but the ketone. This is somewhat unexpected in a supposedly anhydrous solvent but traces of ethanol, acetic acid or water present in the solvent might well be sufficient to decompose the ozonide.

Borsche claims to have prepared two derivatives of this compound although he was not able to isolate the parent ketone. These he obtained by different routes. In the first case (Borsche and Hartmann, Ber., 1940, 73, 839), he attempted to prepare the ketone by the oxidation of 2:3-dihydro-β-quinindine by selenium dioxide.

Distillation of the reaction mixture did not separate any ketone formed from the starting material. From the distillate, however, he prepared a red dinitrophenylhydrazone which darkened and decomposed up to 300°C. This agrees with the derivative prepared from the ozonolysis product although the colour was orange rather than red. However, he obtained only a small quantity and this might well be the 1-keto compound. Our experience of the 1-keto derivative makes it doubtful whether it would have withstood the conditions involved in the reaction.

In the second case (Borsche and Manteuffel, Ann., 1938, 534, 56), Borsche prepared the phenylhydrazone by the following series of reactions:-



The phenylhydrazone was obtained initially as a yellow powder, m.p. 170-173°C which on recrystallisation from benzene-hexane gave orange-red prisms of m.p. 113-114°C. The phenylhydrazone prepared from the ozonolysis product was bright yellow. Recrystallisation from benzene gave bright yellow needles, m.p., 176-177°C agreeing reasonably with their value. Further recrystallisations

from benzene, benzene-hexane or benzene-light petrol did not produce the large depression in melting point or change in colour observed by Borsche. Analyses for these derivatives were on the whole unsatisfactory and so a third derivative was prepared, the oxime, which substantially increases the nitrogen content compared with the parent ketone.

These differences in the derivatives demanded an alternative synthesis of the ketone. Criegie (Ann., 1942, 550, 99) discovered a specific reagent in osmium tetroxide for the oxidation of olefinic double bonds to the corresponding glycol. 3-Benzylidine-dihydro-β-quinindine was treated with osmium tetroxide in ether in the presence of pyridine. The chocolate-coloured adduct was decomposed with mannitol to give the glycol in good yield, analysis confirming the structure. Oxidation of this diol in benzene with lead tetraacetate gave the same product as that obtained from the ozonolysis of the benzylidine compound. Assuming that the starting material for these reactions is in fact the 3-benzylidine derivative of dihydro-β-quinindine, and there is no reason whatsoever to doubt this, then this proves that the ketone is the desired product. Oxidation of the benzylidine derivative with potassium permanganate in acetone at room temperature produced benzoic acid, quinoline-2:3-dicarboxylic acid with a little starting material recovered. This also indicates the ease of oxidation of the ketone. It appears that the starting material is relatively slowly attacked whereas the ketone is further oxidised as soon as it is formed.

3-Keto-dihydro-β-quinindine has unusual solubility properties for a cyclic ketone. It is only slightly soluble in most organic solvents but can be recrystallised readily from ethanol. The ultra-violet absorption spectrum is given in fig. 14. The spectrum of 2-acetylquinoline is not recorded in the literature, only that of 3-acetylquinoline being described. (Eiter and Mirazek, Monats. Chem., 1952, 83, 1491). The infra-red absorption spectrum shows a strong carbonyl absorption at 1717 $cm.^{-1}$

It is known that in the indane series, 1-indanone, on treatment with a Grignard reagent gives rise to a tertiary alcohol which readily dehydrates to give the corresponding indene derivative. (e.g., Elsner and Parker, J.C.S., 1957, 592). It was desirable to carry out the same series of reactions on the ketone synthesised. This would then provide a convenient route to substituted β-quinindines and a possible one for the parent compound. However, in all subsequent reactions with the ketone, a highly insoluble blue material was obtained. These reactions included the Grignard reaction, the Meerwein-Ponndorf-Verley reduction in which acetone was detected, and reduction with borohydride. This blue material is only soluble in acetic acid. It is difficult to offer an explanation as to why no normal products were obtained. Possibly, the proximity of the cyclic nitrogen atom and the ketonic grouping allows interaction as in the case of 8-hydroxyquinoline but this does not account for the production of the blue solid which is probably polymeric.

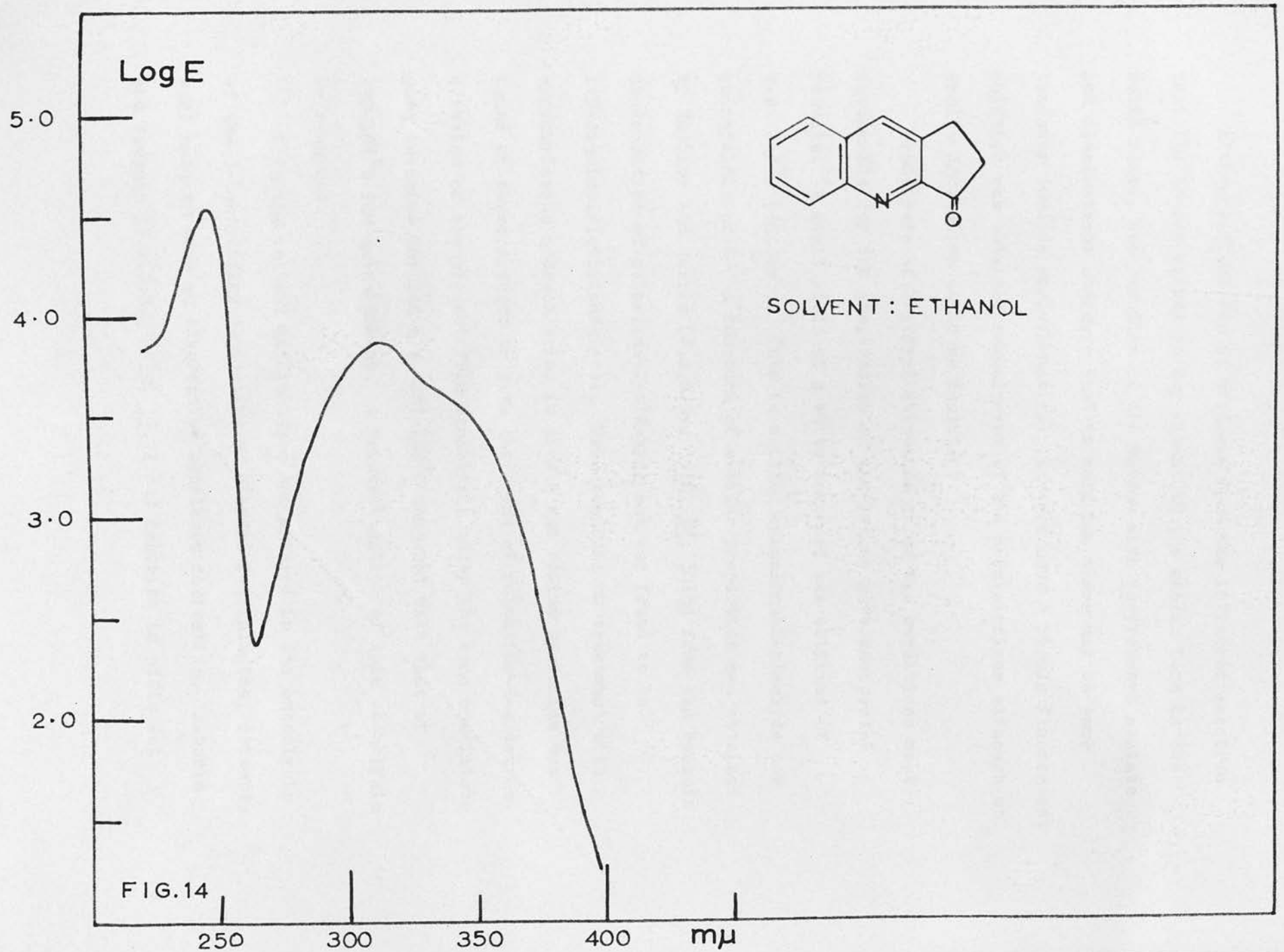


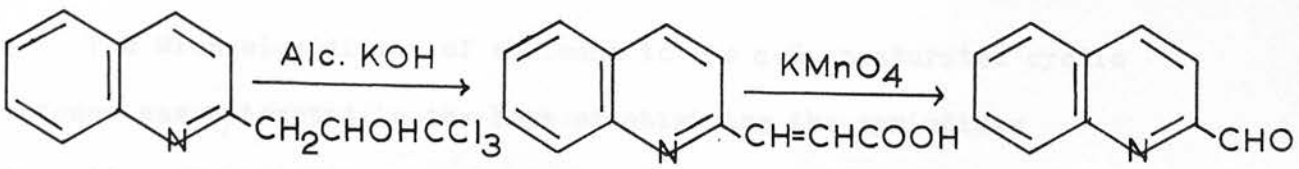
FIG.14

Although there was no evidence from the infra-red spectrum that the ketone exists to any extent in the enolic form in the solid state, the reaction of the ketone with isopropenyl acetate and diazomethane suggests that in solution there may be some tendency towards enol-formation. In each case a highly fluorescent solution was obtained reminiscent of the β-quinindines although no enolic derivative could be isolated.

Ozonolysis of 2-styryl quinoline under the conditions most favourable for the preparation of the ketone gave unexpected results. A small yield of a white compound was obtained of m.p. 218°C (decomp.). This is neither quinoline-2-aldehyde nor quinaldinic acid. A compound of similar properties was obtained by Buehler and Harris (J.A.C.S., 1950, 72, 5015) from the benzoin condensation of quinoline-2-aldehyde and was found to be 1:2-diquinolylethyleneglycol. This compound on treatment with hydroxylamine hydrochloride in dioxan and sodium hydroxide was found by these authors to give the oxime of quinoline-2-aldehyde. Reaction of the product from ozonolysis under the same conditions gave an oxime but had m.p. 167-168°C compared with that of 190-191°C for quinaldoxime. A reinvestigation of this ozonolysis is required.

With the initial difficulties encountered in the ozonolysis of the 3-benzylidine derivative of dihydro-β-quinindine, attempts were made to make an alternative ethylenic derivative. Alberts and Bachman (J.A.C.S., 1935, 57, 1284) describe an efficient

procedure for the condensation of quinaldine and chloral. The following series of reactions have been described for the condensation product:-



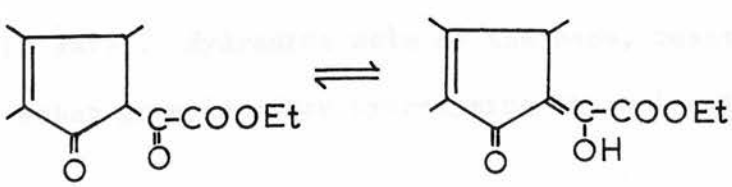
The condensation of chloral and dihydro-β-quinindine in pyridine proceeded in a satisfactory yield. The hydrolysis, however was not successful (c.f. Einhorn, Ann., 1895, 287, 27). The addition of the condensation product to ethanolic potassium hydroxide gave a green solution which turned to vivid blue on boiling. No acidic or any other product could be isolated and characterised; the reaction was not further investigated although it would appear to be worthy of study in the future.

Some preliminary investigations were carried out on possible syntheses of the β-pyrindine system. Stobbe and Volland (Ber., 1902, 35, 3973) added chalcone to cyclopentanone and cyclised the product with hydroxylamine hydrochloride to give 2:4-diphenyl-6:7-dihydro-β-pyrindine. This was repeated but in no instance could the cyclisation be carried out in the yield quoted. Better results were obtained by refluxing the components in butanol. Anticipating success in the β-quinindine series, conditions for the condensation of the product with benzaldehyde were examined.

No condensation was observed under the conditions employed for β-quinindine. It was found that the reaction took place when the reactants were heated together at 200°C in the presence of anhydrous zinc chloride.

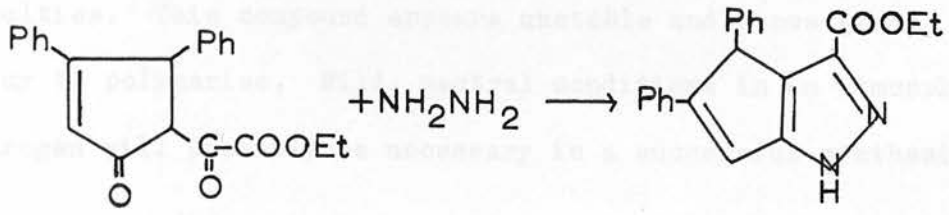
The Michael addition of chalcone to the α-β unsaturated cyclic ketones was attempted in the hope of obtaining the pyrindines directly. No reaction was observed and only starting materials were recovered. This addition was found to proceed, however, with a substituted cyclopentanone, in good yield and the resulting 1:5-diketone could be cyclised to the substituted dihydro-β-pyrindine. A similar reaction was carried out involving the decomposition of β-dimethylaminopropiophenone in phenylcyclopentanone resulting in β-acylethylation of the ketone and formation of the 1:5-diketone (Gill et al., J.A.C.S., 1952, 74, 4923).

An alternative possible synthesis of the β-pyrindines employing the α-β unsaturated cyclic ketones is the adaption of the reaction described in reaction schemes I and II (p.29) due to Thompson and Basu. Formylation of these unsaturated ketones under those conditions applied to cyclopentanone and 1-indanone did not yield the desired derivative. It was thought that the same reactions might be carried out by using the closely related derivatives, the pyruvic esters, having the formula:



The enolic state is equivalent to that of the analogous formyl derivative. Cyclopentenone and 3:4-diphenylcyclopentenone reacted with diethyl oxalate giving the pyruvic esters. Neither with cyanoacetamide nor ethyl β-aminocrotonate did the reaction give a substituted pyrindine.

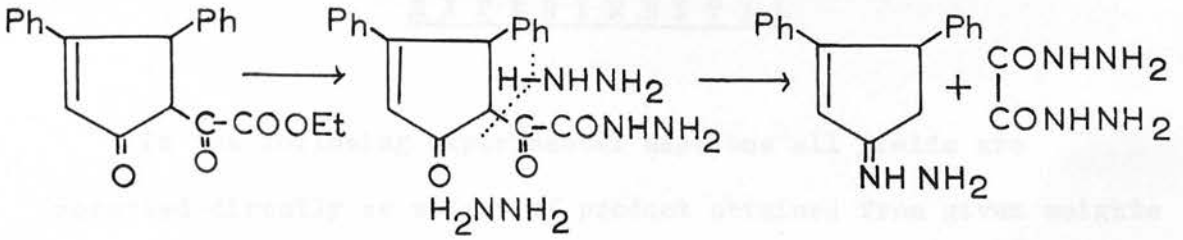
Compounds related to those described in the next section could be expected from the reaction of these esters with hydrazine.



The reaction was abnormal in that treatment of the pyruvic ester with hydrazine hydrate in ethanol gave a quantitative yield of oxalic dihydrazide. The other product isolated was 3:4-diphenylcyclopentenone hydrazone. This is a reverse Claisen condensation. The reversibility of the acetoacetic ester condensation is well established. This can, however, be considered from a different viewpoint. Derivatives of acetoacetic ester undergo "ketonic" fission with dilute acid or alkali.

$$CH_3CO\,CH_2COOEt \longrightarrow CH_3COCH_3 + CO_2 + EtOH$$

The pyruvic ester can be considered to be a derivative of acetoacetic ester. Hydrazine acts as the base, reacting first with free ester grouping then hydrolysing the molecule as above.



From this experimental work, it can be concluded that synthesis of the parent β-quinindine will involve considerable difficulties. This compound appears unstable and shows great tendency to polymerise. Mild, neutral conditions in an atmosphere of nitrogen will probably be necessary in a successful synthesis.

EXPERIMENTAL

In the following experimental sections all yields are reported directly as weight of product obtained from given weights of starting materials.

All melting points were determined by means of a Kofler micro-melting point apparatus.

Chromatographic separations were carried out on columns prepared from Activated Alumina Type "H", supplied by Peter Spence & Sons Ltd., Widnes.

Spectral determinations were made using a Unicam SP500 spectrophotometer and with 10mm. silica cells.

Analyses were performed by Drs. Weiler and Strauss, Oxford.

Preparation of 2:3-dihydro-β-quinindine-9-carboxylic acid.

Borsche, Ann., 1910, 377, 121

Isatin (40 g.) and cyclopentanone (46 g.) gave 2:3-dihydro-β-quinindine-9-carboxylic acid (52 g., 90%).

Preparation of methyl 2:3-dihydro-β-quinindine-9-carboxylate.

2:3-Dihydro-β-quinindine-9-carboxylic acid (22 g.) in absolute methanol (300ml.) and concentrated sulphuric acid (50ml.) were boiled under reflux for 48 hours. The solution was poured into excess sodium carbonate solution and extracted with ether. The extract was dried over anhydrous sodium sulphate and the solvent removed leaving an oil which slowly crystallised to a buff-coloured solid. Crystallisation from aqueous methanol gave methyl 2:3-dihydro-β-quinindine-9-carboxylate (29g.) as colourless prisms, m.p. 74-75°C. (Found: C,73.7; H,5.9; N,5.9. $C_{14}H_{13}NO_2$ requires C,73.9; H,5.7; N,6.2%).

Preparation of 2:3-dihydro-β-quinindine.

A round-bottomed flask containing 2:3-dihydro-β-quinindine-9-carboxylic acid (52g.) was set up for vaccuum distillation. Vaccuum was applied throughout the reaction. Gentle, direct heating caused the solid to liquify with a vigorous ebullition of carbon dioxide. When decarboxylation was complete, heating was increased and the residue distilled. The distillate was dissolved in ether, the extract washed with sodium carbonate solution and

water and dried over anhydrous sodium sulphate. Removal of the solvent gave a dark, viscous oil which was distilled under reduced pressure to give 2:3-dihydro-β-quinindine (30g., 71%) as a colourless crystalline mass, m.p. 59-60°C. (Borsche gives m.p. 59-60°C.)

Bromination of methyl dihydro-β-quinindine-9-carboxylate.

The ester (6.2g.) was dissolved in dry carbon tetrachloride (100ml.) and N-bromosuccinimide (4.9g.) and benzoyl peroxide (0.15g.) added. The solution was boiled under reflux for 1.5 hours giving a dark brown solution. After cooling, the succinimide was filtered off (2.7g.) and the solvent removed. Attempts to distil the residue, a dark oil, at reduced pressure resulted in the formation of a blue-black polymer, slightly soluble in acetone and ethanol. (Found: C,57.0; H,3.6; N,4.1; Br,14.9%). This corresponds roughly to four molecules of β-quinindine ester.

Reactions of 3-bromo-2:3-dihydro-β-quinindine-9-carboxylate.

The bromo derivative prepared as above was employed without further purification.

1. The bromo compound was taken up in methanol and added to a 10% methanolic potassium hydroxide solution. The solution darkened and black tars were deposited on the walls of the flask. No pure product could be isolated.

2. A benzene solution of the bromo compound was treated with pyridine and allowed to stand overnight. The crystals were collected

and washed with ether. Crystallisation from methanol/ether gave colourless needles of the pyridinium bromide m.p. 164-165°C. (decomp.). High vaccuum distillation of this salt gave a blue-black polymer and pyridine was detected in the cold trap.

Preparation of 3-phenylcyclopent-2:3-en-1-one.

Mousseron and Rouzier, Bull. Soc., 1953, 190.

Ethyl phenacylacetoacetate (56g.) gave 3-phenylcyclopent-2:3-en-1-one, (32g., 90%), m.p. 76-77°C. Borsche and Fels (Ber., 1906, 39, 1922) give m.p. 82-83°C.

The 2:4-dinitrophenylhydrazone derivative was prepared in the usual manner. It crystallised from glacial acetic acid in dark red prisms m.p. 255-257°C. (Found: C,60.4; H,4.5; N,15.8. $C_{17}H_{14}N_4O_4$ requires C,60.5; H,4.2; N,16.6%).

Reaction of 3-phenylcyclopentenone with isatin.

c.f., Borsche, Ann., 1910, 377, 121.

Solutions of isatin (5.3g.) in 30% potassium hydroxide solution (30ml.) and 3-phenylcyclopentenone (5.0g.) in ethanol (65ml.) were mixed. After boiling under reflux for six hours, the ethanol was removed by distillation under reduced pressure. The solution was diluted with water (200ml.) and filtered to remove a little dark solid. After cooling, the solution was acidified with 50% acetic acid to give a green-yellow precipitate. The solid was collected on a filter and washed with water (500ml.) and ethanol (50ml.).

The 2-phenyl-β-quinindine-9-carboxylic acid (7g., 77.5%) is pure enough for most purposes but may be recrystallised from pyridine as fine yellow needles decomposing between 260 and 290°C. (Found: C,75.0; H,4.9; N,4.1. $C_{19}H_{13}NO_2.H_2O$ requires C,74.7; H,4.9; N,4.6%).

Methylation of 2-phenyl-β-quinindine-9-carboxylic acid.

2-Phenyl-β-quinindine-9-carboxylic acid (1g.) was dissolved in absolute methanol (35ml.) containing concentrated sulphuric acid 1.5ml.) and the solution boiled under reflux overnight. After pouring into sodium carbonate, the solution was extracted with ether to give an intensely blue fluorescent solution. The extract was washed with water and dried over anhydrous sodium sulphate. Removal of the solvent gave an oil which slowly solidified to a yellow crystalline mass. Recrystallisation from methanol gave methyl 2-phenyl-β-quinindine-9-carboxylate (0.3g., 29%) as colourless prisms, m.p. 135-136°C. (Found: C,79.7; H,4.9; N,4.4. $C_{20}H_{15}NO_2$ requires C,79.7; H,5.0; N,4.7%).

Reaction of 2-phenyl-β-quinindine-9-carboxylic acid with diazomethane.

2-Phenyl-β-quinindine-9-carboxylic acid was added to an excess of diazomethane in dry ether. Only a slow evolution of nitrogen was observed. The acid disappeared within 4 hours and the solution was intense red-purple in colour. After filtering, the solution was taken to dryness and extracted with petrol-ether (b.p. 40-60°C).

This extract deposited colourless crystals leaving a vivid blue supernatent. The supernatent was decanted from the crystals and these treated separately.

(a) The crystals were recrystallised from methanol giving colourless prisms, m.p. 135-136°C which was not depressed on admixture with methyl 2-phenyl-β-quinindine-9-carboxylate.

(b) The petrol-ether extracts were taken to dryness and the residue taken up in benzene. Chromatography in benzene separated a green band from a colourless band which had a strong blue fluorescence in ultra-violet light. Elution with benzene gave the green band as a vivid blue solution and the colourless band as a fluorescent, colourless solution. The colourless solution gave more methyl 2-phenyl-β-quinindine-9-carboxylate. The benzene was removed from the blue solution to give a green oil which was dissolved in hot methanol and added to a hot methanolic solution of T.N.B. On cooling, crystals separated which were collected and recrystallised from methanol to give brown-black needles, m.p. 154-155°C. (Found: C,61.2; H,3.8; N,10.2. $C_{27}H_{20}N_4O_8$ requires C,61.4; H,3.8; N,10.6%). This is the T.N.B. complex of anhydro-2-phenyl-N-methyl-β-quinindine-9-carbomethoxylate hydroxide. All attempts to crystallise the anhydro salt failed.

Preparation of the methoiodide of methyl 2-phenyl-β-quinindine-9-carboxylate.

The methyl ester in benzene was boiled under reflux with an

excess of methyl iodide for 3 hours. The methoiodide separated from the solution as a yellow amorphous solid, the supernatent being a blue-green. The solid was collected and crystallised from aqueous methanol as yellow prisms which started darkening at 215°C but had not melted at 320°C. (Found: C,57.1; H,4.4; N,2.6; I,22.2. $C_{21}H_{18}NO_2I$ requires C,56.9; H,4.1; N,3.2; I,28.6%).

Preparation of the anhydro salt from methyl 2-phenyl-β-quinindine-9-carboxylate-N-methoiodide.

A suspension of the methoiodide in 10% aqueous sodium carbonate solution was shaken with chloroform. The chloroform extract which was a vivid blue colour was dried over anhydrous sodium sulphate. After removing the solvent, the residue was taken up in hot methanol and added to a hot methanolic solution of T.N.B. The solution deposited brown crystals on cooling which were recrystallised from methanol as brown-black needles, m.p. 154-155°C. A mixed melting point with the T.N.B. complex obtained from the diazomethane reaction above showed no depression.

Preparation of anhydroacetonebenzil.

Japp and Knox, J.C.S., 1905, 87, 673.

Benzil (250g.) and acetone (156g.) gave anhydroacetonebenzil (240g., 80%).

The semicarbazone derivative, prepared in the usual way, was recrystallised from ethanol as colourless cubes m.p. 235-236°C.

(Found: C,70.2; H,6.0; N,13.9. $C_{18}H_{17}N_3O_2$ requires C,70.3; H,5.6; N,13.7%).

Preparation of 3:4-diphenylcyclopent-2:3-en-1-one.

Koelsch and Geissman, J.Org. Chem., 1938, 3, 489. Anhydroacetonebenzil (200g.) gave diphenylcyclopentenone (86g., 46%). The semicarbazone which crystallised from methanol as colourless prisms, had m.p. 215-216°C (decomp.). This compound turns yellow on exposure to light. Wiedlich (Ber., 1941, 74, 1195) gives m.p. 219°C. (decomp.).

Preparation of 1:2-diphenyl-β-quinindine-9-carboxylic acid.

Diphenylcyclopentenone (20g.) in ethanol (160ml.) was added to isatin (18g.) in 30% potassium hydroxide solution (80ml.). The solution was boiled under reflux for 7 hours and the ethanol then removed by distillation under reduced pressure. After dilution with water (250ml.) and filtering, the solution was acidified with 50% acetic acid to give a copious yellow precipitate. Precipitation was complete after 5 hours. The solid was collected and washed with water (500ml.) and ethanol (50ml.). The 1:2-diphenyl-β-quinindine-9-carboxylic acid (20g., 65%) is pure enough for most purposes but may be recrystallised from pyridine to give bright yellow needles m.p. 282-284°C. (Found: C,75.3; H,5.7; N,3.4. $C_{25}H_{17}NO_2.2H_2O$ requires C,75.2; H,5.3; N,3.5%).

Methylation of 1:2-diphenyl-β-quinindine-9-carboxylic acid.

1:2-Diphenyl-β-quinindine-9-carboxylic acid (5.8g.) in absolute methanol(150ml.) and concentrated sulphuric acid (25ml.) was boiled under reflux for 2 days. The solution was then poured into excess 10% sodium carbonate solution and extracted with ether. The blue fluorescent extract was washed with water and dried over anhydrous sodium sulphate. Removal of the solvent gave a yellow solid (4.1g., 79%) which was crystallised from benzene-petrol ether (b.p. 60-80°C.) as pale yellow needles m.p. 170-172°C. (Found: C,83.0; H,4.7; N,3.3. $C_{26}H_{19}NO_2$ requires C,82.8; H,5.1; N,3.7%).

Reaction of 1:2-diphenyl-β-quinindine-9-carboxylic acid with diazomethane.

The acid was suspended in ether and an etherial solution of diazomethane added. There was an immediate evolution of nitrogen and the solution became green in colour. After standing overnight, the solution was filtered and the solvent removed to give a green oil. Chromatography of a solution of this oil in benzene and elution with benzene removed a yellow band. Further elution with benzene/ether (1:1) removed a green band which gave a vivid blue solution.

The yellow solution was evaporated to dryness and the residue crystallised from benzene-petrol ether (b.p. 60-80°C.) as pale yellow needles m.p. 171-173°C which did not depress the melting point of methyl 1:2-diphenyl-β-quinindine-9-carboxylate.

The blue solution yielded a green-blue oil on removal of the

solvent which crystallised on the addition of methanol. Recrystallisation from methanol gave black prisms m.p. 178-179°C. (Found: C,82.9; H,5.1; N,3.7. $C_{27}H_{21}NO_2$ requires C,82.8; H,5.4; N,3.6%). This is anhydro-1:2-diphenyl-N-methyl-β-quinindine-9-carbomethoxylate hydroxide.

Attempts to form the T.N.B. complex in methanol failed but the complex readily formed in ethanol. Recrystallisation from ethanol, however, caused the complex to dissociate and recrystallisation was only possible from a solution of ethanol saturated with T.N.B. which gave black prisms, m.p. 130-132°C. (Found: C,67.0; H,3.8; N,8.5. $C_{33}H_{24}N_4O_8$ requires C,65.6; H,4.0; N,9.3%). It appears that on recrystallisation some dissociation had taken place.

Preparation of the methoiodide of methyl 1:2-diphenyl-β-quinindine-9-carboxylate.

The ester (1g.) in benzene (25ml.) and methyl iodide (5ml.) were boiled under reflux for 3 hours. The orange precipitate (1.1g.) was collected and recrystallised from methanol/ether decomposing at 215°C. (Found: C,62.7; H,4.6; N,2.4; I,19.4. $C_{27}H_{22}NO_2I$ requires C,62.5; H,4.2; N,2.7; I,24.5%).

Preparation of the anhydro salt from methyl 1:2-diphenyl-β-quinindine-9-carboxylate-N-methoiodide.

A suspension of the methoiodide in 10% sodium carbonate solution was shaken with chloroform. The vivid blue chloroform extract was

dried over anhydrous sodium sulphate and the solvent removed. On adding methanol to the residue, the oil crystallised and was recrystallised from methanol as black prisms m.p. 177-178°C. The melting point was not depressed on admixture with the product derived from the action of diazomethane on the acid. The yield is quantitative.

Hydrogen chloride was passed into an etherial solution of the anhydro salt. The yellow precipitate was collected and recrystallised from methanol-ether as yellow prisms, m.p. 120-122°C. (Found: C,72.6; H,5.7; N,3.0; Cl,5.7. $C_{27}H_{22}NClO_2$ requires C,72.7; H,5.4; N,3.1; Cl,8.0%).

Decarboxylation of 1:2-diphenyl-β-quinindine-9-carboxylic acid.

The acid (0.5g.) was intimately ground with soda-lime (2g.) and placed in a hard-glass tube. Finely ground soda-lime (1g.) was then placed above the mixture. The tube was attached to a U-tube immersed in ice-water which was attached to the water pump. Suction was applied and the tube heated, gently at first, then strongly. A buff solid collected in the U-tube which was extracted into ether. The extract was washed with sodium carbonate solution and dried over anhydrous sodium sulphate. Removal of the solvent left a buff solid which was crystallised from ethanol as fine colourless needles, (0.1g.), m.p. 187-188°C. (Found: C,90.0; H,5.8; N,4.4. $C_{24}H_{17}N$ requires C,90.3; H,5.3; N,4.4%).

The picrate was prepared in ethanolic solution and the yellow

solid recrystallised from glacial acetic acid as bright yellow prisms, m.p. 197-198°C. (decomp.). (Found: C,65.8; H,3.8; N,14.0. $C_{30}H_{20}N_4O_7$ requires C,65.7; H,3.7; N,10.2%).

Preparation of the methoiodide of 1:2-diphenyl-β-quinindine.

1:2-Diphenyl-β-quinindine in benzene was boiled under reflux for 3 hours. A yellow, amorphous solid was precipitated which was recrystallised from chloroform-ether as yellow prisms, m.p. 193-194°C. (decomp.).

Preparation of the anhydro salt from 1:2-diphenyl-β-quinindine-N-methoiodide.

The methoiodide was suspended in 10% sodium carbonate solution and shaken with chloroform. The blue extract was dried over anhydrous sodium sulphate. Removal of the solvent gave a blue residue which was dissolved in hot methanol and added to a hot methanolic solution of T.N.B. Recrystallisation of the complex from methanol gave black prisms, m.p. 181-182°C. (Found: C,68.2; H,4.0; N,9.9. $C_{31}H_{22}N_4O_6$ requires C,68.1; H,4.0; N,10.3%).

Decarboxylation of 2-phenyl-β-quinindine-9-carboxylic acid.

The same procedure was adopted as used for the decarboxylation of the diphenyl derivative. The product, however, collected not in the U-tube but at the top of the decarboxylating tube. The solid was extracted into ether, the extract washed with sodium carbonate solution and water and dried over anhydrous sodium sulphate. The

residue after removal of the solvent consisted of a very dark solid which could not be purified. It was therefore converted directly to its methoiodide by boiling under reflux for two hours a solution in benzene with methyl iodide. The greenish-yellow solid which separated was collected and recrystallised from ethanol-ether as yellow-green prismatic needles, m.p. 203-205°C.

Preparation of the anhydro salt from 2-phenyl-β-quinindine-N-methoiodide.

The above methoiodide was suspended in sodium carbonate solution and shaken with chloroform. The reddish-purple extract was dried and the chloroform removed. The oily residue was dissolved in hot methanol and added to a hot methanolic solution of T.N.B. Crystals separated on cooling which were collected and recrystallised from methanol as black prisms, m.p. 144-145°C. (Found: C,63.7; H,3.6; N,12.6. $C_{25}H_{18}N_4O_6$ requires C,63.8; H,3.8; N,11.9%).

Preparation of 2-phenylbenzocyclopentapyran.

Boyd, Chem. and Ind., 1957, 1244.

5-Salicylidine-3-phenylcyclopent-2-enone (5g.) in acetic acid (45ml.) and concentrated hydrochloric acid (5ml.) was heated on a water bath for 0.5 hours. The solution was poured into water (300ml.) and the 2-phenylbenzocyclopentapyran collected in quantitative yield. Crystallisation from benzene gave brownish-purple prisms, m.p. 208-209°C. (Boyd gives m.p. 207-207.5°C.)

Preparation of 1:2-diphenylbenzocyclopentapyran.

3:4-Diphenylcyclopentenone (3g.) and salicylaldehyde (1.6g.) in ethanol (50ml.) in the presence of a small quantity of piperidine acetate were boiled under reflux for 3 hours. The red colour of the solution indicated that the salicylidine derivative had partially cyclised to the pyran. Removal of the ethanol gave a red oil which, without further purification, was taken up in acetic acid (45ml.) and concentrated hydrochloric acid (5ml.). After heating on a water bath for 2 hours, the solution was poured into water (250ml.) to give a purple-coloured precipitate. This was collected, thoroughly washed with water and dried over phosphorous pentoxide. The solid (3g., 73%) was recrystallised from ethanol as blue-black prisms which were dark red by transmitted light, m.p. 155-156°C. (Found: C,88.8; H,5.0. $C_{24}H_{16}O$ requires C,90.0; H,5.0%).

Preparation of cyclopent-2:3-en-1-one.

Alder and Flock, Ber., 1956, 1732.

Cyclopentadiene (355g.) gave cyclopentenone (200g.) b.p. 39°C at 7mm. pressure.

Reaction of isatin with cyclopentenone.

Cyclopentenone (11.2g.) in ethanol (80ml.) was added to isatin (10g.) in 30% potassium hydroxide solution and the mixture allowed to stand at room temperature for 2 days. The solution was then diluted with water (100ml.) and acidified with 50% acetic acid. The yellow

amorphous solid was collected and washed with water. This material (12.5g.) could not be crystallised and all attempts to methylate it failed.

Condensation of cyclopentenone and isatin in the presence of piperidine.

Isatin (10g.), cyclopentenone (5.6g.) and piperidine (1ml.) in absolute ethanol (250ml.) were allowed to stand overnight. A yellow crystalline solid (1.5g.) had separated and was collected. The filtrate deposited a further quantity (2.0g.) after standing a further day. Crystallisation from ethanol gave a white amorphous solid, decomposing at 295-330°C. (Found: C,66.8; H,4.4; N,7.7. $C_{21}H_{16}N_2O_5$ requires C,67.0; H,4.3; N,7.5%). This corresponds to two molecules of isatin and one molecule of cyclopentenone. The product was not further investigated.

Condensation of cyclopentanone and isatin in the presence of piperidine.

Isatin (1g.), cyclopentanone (0.6g.) and piperidine (0.15ml.) in absolute ethanol (25ml.) were allowed to stand overnight at room temperature. A small quantity of yellow solid was collected and recrystallised from ethanol. The white amorphous solid did not melt below 300°C. (Found: C,66.6; H,4.9; N,7.6. $C_{21}H_{18}N_2O_5$ requires C,66.7; H,4.8; N,7.4%). This again corresponds to two molecules of isatin for each molecule of cyclopentanone.

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Reduction of 3-phenylcyclopent-2:3-en-1-one.

Mousseron and Rouzier, Bull. Soc., 1953, 190.

3-Phenylcyclopentenone (20g.) in absolute ethanol (150ml.) was reduced catalytically at room temperature and atmospheric pressure in the presence of 2.5% palladium on calcium carbonate (10g.). 3.2 litres of hydrogen were absorbed in 3 hours. The solution was filtered and the ethanol removed under reduced pressure. 3-Phenylcyclopentanone (19g.) distilled at an oil-bath temperature of 120°C and 5mm. pressure.

The dinitrophenylhydrazone crystallised as orange plates from benzene, m.p. 155-156°C. (Mousseron and Rouzier give m.p. as 154-155°C.)

Reaction of 3-phenyl-1-cyclopentanone with isatin.

3-Phenylcyclopentanone (8.5g.) in ethanol (80ml.) was added to isatin (7.8g.) in 30% potassium hydroxide solution (40ml.) and boiled under reflux overnight. The ethanol was then removed by distillation, the solution diluted with water (250ml.) and acidified with 50% acetic acid. The pale yellow solid was collected and washed with water. Recrystallisation from ethanol gave a buff-coloured solid (10.2g., 62%), m.p. 239-240°C.(decomp.). (Found: C,78.8; H,5.4; N,4.6. $C_{19}H_{15}NO_2$ requires C,78.9; H,5.2; N,4.8%).

Methylation of the acid obtained from the reaction of 3-phenylcyclopentanone with isatin.

The acid (3g.) was added to a solution of diazomethane (0.8g.)

in ether. There was a vigorous evolution of nitrogen and the mixture was allowed to stand overnight. Excess diazomethane was destroyed by the addition of acetic acid and the ether then washed with sodium carbonate solution and dried. The residue, after evaporation of the solvent, was dissolved in benzene and chromatographed. Elution with benzene removed a colourless band which had a strong blue fluorescence in ultra-violet light. Removal of the solvent gave a white solid (1.75g., 56%) which crystallised from petrol ether (b.p. 40-60°C.) as colourless prisms, m.p. 103-104°C. (Found: C,79.1; H,5.5; N,4.2. $C_{20}H_{17}NO_2$ requires C,79.2; H,5.6; N,4.6%). A much poorer yield of the ester is obtained by the use of methanol-sulphuric acid.

Reduction of methyl 2-phenyl-β-quinindine-9-carboxylate.

The ester (0.9g.) was dissolved in ethanol (100ml.) and reduced catalytically in the presence of Adams' catalyst (25mg.) at room temperature and atmospheric pressure. The reduction stopped after the uptake of 60ml. of hydrogen. The ethanol was then removed and the residue chromatographed in benzene. Elution with benzene removed a colourless band which had a blue fluorescence in ultra-violet light. After removing the solvent, the solid was recrystallised from petrol ether (b.p. 40-60°C.) and had m.p. 103-104°C. Mixed m.p. with the ester obtained above, showed no depression.

Attempted bromination-dehydrobromination of methyl 2-phenyl-dihydro -β-quinindine-9-carboxylate.

The ester (1.0g.) was boiled under reflux with N-bromosuccinimide (0.6g.) in carbon tetrachloride (50ml.) for 0.5 hours. The solution was cooled and filtered. Removal of the carbon tetrachloride left an oily residue which was used without further purification. Attempted dehydrobromination with either methanolic potassium hydroxide or pyridine gave as the only product to be isolated, a red amorphous solid, m.p. 205-210°C. This was not further investigated.

Condensation of dihydro-β-quinindine and benzaldehyde.

Dihydro-β-quinindine (30g.) and freshly distilled benzaldehyde (50g.) were heated in an oil bath at 150°C for four hours, provision being made that the water formed in the reaction could distil from the reaction mixture. The excess benzaldehyde was then removed by distillation and the residue triturated with ethanol (30ml.). The solid which formed was collected and recrystallised with carbon screening from ethanol in which it had a strong blue fluorescence. The 3-benzylidine-dihydro-β-quinindine (29g., 64%) was obtained as colourless needles, m.p.119-120°C. (Found: C,88.7; H,5.9; N,5.4. $C_{19}H_{15}N$ requires C,88.7; H,5.8; N,5.4%).

The benzylidine derivative was heated for three hours on a water bath with excess dimethyl sulphate. Addition of excess ether caused the precipitation of a bright yellow solid. This was recrystallised from ethanol as bright yellow prisms, m.p. 288-289°C (decomp).

(Found: C,65.1; H,5.2; N,3.7; S,8.8. $C_{21}H_{21}NSO_4$ requires C,65.8; H,5.5; N,3.7; S,8.4%. $C_{20}H_{19}NSO_4$ requires C,65.0; H,5.2; N,3.8; S,8.7%). This is the salt of the benzylidine compound and methylhydrogen sulphate and was proved by the regeneration of the benzylidine compound on treatment with alkali.

For the preparation of the N-methyl methosulphate, it was found necessary to employ carefully purified dimethyl sulphate. The benzylidine compound (0.5g.) in dimethyl sulphate (10ml.) was heated on a water bath for 3 hours. The solution was then poured into ether, the yellow solid (0.75g., 100%) collected and recrystallised from ethanol as yellow plates m.p. 170-220°C. (Found: C,65.6; H,5.4; N,3.6; S,8.5. $C_{21}H_{21}NSO_4$ requires C,65.8; H,5.5; N,3.7; S,8.4%).

The benzylidine methoiodide was prepared by treating an ethanolic solution of the methosulphate with an ethanolic solution of lithium iodide. The yellow solid was recrystallised from aqueous ethanol as yellow prisms, m.p. 254-255°C. (decomp.). (Found: C,59.7; H,4.6; N,3.4; I,32.7. $C_{20}H_{18}NI$ requires C,60.1; H,4.5; N,3.5; I,31.8%).

Ozonolysis of 3-benzylidine-dihydro-β-quinindine.

1. In acetic acid solution.

Ozonised oxygen (c.5%) was passed through a solution of the benzylidine compound (1g.) in glacial acetic acid (50ml.) contained in a wash bottle for one hour. The solution had passed from a deep

to a very pale yellow colour. After pouring into water (250ml.), zinc dust (2g.) was added and the solution slowly heated to 90°C. Concentrated hydrochloric acid (5ml.) was added and the solution steam-distilled.

(a) Steam-distillate.

The steam-distillate (150ml.) was extracted with ether and the ether removed to give a milky residue. The residue formed a dinitrophenylhydrazone which was recrystallised from ethanol as orange needles, m.p. 235-236°C. Mixed m.p. with an authentic sample of benzaldehyde 2:4-dinitrophenylhydrazone, 236-237°C.

(b) Residue.

The residue was neutralised with sodium carbonate and extracted with ether. The extract was dried and the solvent removed to give a yellow solid. Recrystallisation from ethanol with carbon screening gave colourless plates (0.1g.), m.p. 183-184°C. with decomposition.

This compound was a ketone and formed a dinitrophenylhydrazone which crystallised from acetic acid as yellow-orange fine needles which decomposed between 275 and 295°C.

Several repetitions of this experiment produced none of the ketone although benzaldehyde was detected in each case.

2. <u>In anhydrous carbon tetrachloride</u>.

The benzylidine derivative (1g.) was dissolved in anhydrous carbon tetrachloride (50ml.) and ozonised oxygen (c.5%) passed through the solution for one hour. A copious white solid had

separated from the solution. Water (10ml.) was added and the solvent removed cautiously under reduced pressure. Dark material was deposited on the sides of the flask. More water (50ml.) was added and the solution gently warmed. Extraction with ether, and removal of the solvent gave a yellow solid (0.1g.) which had m.p. 183-184°C after recrystallisation from ethanol.

3. In anhydrous ethyl acetate.

The procedure giving the best results was found to be as follows. The benzylidine derivative (2g.) in anhydrous ethyl acetate (80ml.) was ozonised for 40 minutes. To obtain good results, the ozonolysis must be stopped as soon as ozone is detected in the issuing oxygen by starch-iodide paper since over-oxidation readily occurs. Nitrogen was then bubbled through the solution for 15 minutes to remove dissolved ozone and oxygen. Adams' catalyst (25mg.) was added and hydrogen bubbled through the solution for one hour. Ethanol (25ml.) was added, the solution heated to boiling and filtered. Removal of the solvents gave a yellow residue which, when crystallised from ethanol, gave colourless plates, (0.9g., 64%) m.p. 183-184°C. This is the same ketone as obtained in 1. (Found: C,77.6,77.8,77.4; H,4.8, 5.2,4.7; N,8.0,7.6,6.7. $C_{12}H_9NO$ requires C,78.7; H,4.9; N,7.7%). Dinitrophenylhydrazone: crystallised as yellow-orange needles from acetic acid decomposing between 275 and 295°C. (Found: C,57.5,57.7,57.5; H,3.9,4.8,3.8; N,17.5,18.2,18.8. $C_{18}H_{13}N_5O_4$ requires C,59.5; H,3.6; N,19.3. $C_{18}H_{13}N_5O_4 \cdot 1/2\ H_2O$ requires C,58.1; H,3.8; N,18.8%).

Phenylhydrazone: crystallised as yellow needles from benzene, m.p. 176-177°C. (Found: C,78.3,78.0; H,6.0,5.7; N,11.5. $C_{18}H_{15}N_3$ requires C,79.1; H,5.5; N,15.4%).

Oxime: crystallised from ethanol as colourless prisms, m.p. 230-232°C (decomp.). (Found: C,72.2; H,4.6; N,11.8. $C_{12}H_{10}N_2O$ requires C,72.8; H,5.0; N,14.1%).

The analyses for the ketone and its derivatives are on the whole unsatisfactory. The percentage of carbon found is slightly low in all cases. It would also appear that one of the nitrogen atoms, probably the ring nitrogen, is difficult to analyse. However, the analyses, taken together, do exclude any other possible structure for the ketone.

Oxidation of 3-benzylidine-dihydro-β-quinindine with osmium tetroxide.

To the benzylidine compound (2g.) in anhydrous ether (200ml.) containing anhydrous pyridine (5ml.) was added osmium tetroxide (1g.) and the mixture allowed to stand at room temperature for three hours. The chocolate-brown crystalline precipitate (2.37g.) was collected and washed with ether.

The precipitate was added to a mixture of potassium hydroxide (1g.) and mannitol (10g.) in water (100ml.) and chloroform (30ml.). After shaking for one day, the chloroform layer was separated, dried and the solvent removed to give a solid residue. A petrol ether (b.p.40-60°C) extract precipitated a white solid which was recrystallised from benzene-isooctane as small white plates, m.p. 139-140°C.

(Found: C,78.1; H,6.0; N,4.7. $C_{19}H_{17}NO_2$ requires C,78.3; H,5.8; N,4.8%).

Oxidation of cis 3-hydroxy-3-(α-hydroxybenzyl)-dihydro-β-quinindine with lead tetraacetate.

The glycol (0.22g.) and lead tetraacetate (0.33g.) in benzene (50ml.) were shaken for three hours. The benzene was removed by distillation and the residue crystallised from ethanol as colourless plates, m.p. 183-184°C. (decomp.). A mixed m.p. with the ozonolysis product had m.p. 184-185°C. (decomp.).

Reactions of 3-keto-dihydro-β-quinindine.

1. Grignard reaction.

The ketone (0.5g.) in benzene (100ml.) was added to phenylmagnesium bromide (from 0.25g. magnesium and 1.72g. bromobenzene) in ether (100ml.) during 0.5 hours. The mixture was boiled under reflux for three hours during which time a pink solid separated. The complex was decomposed with 50% hydrochloric acid (100ml.) and ice (20g.). The aqueous phase was then basified with ammonia after adding ammonium chloride (15g.) to the solution. A blue solid was precipitated which was insoluble in ethanol, ether and chloroform. No other product could be isolated.

2. Meerwein-Pondorf-Verley reduction.

The ketone (0.19g.) was added to aluminium isopropoxide (0.67g.)

in isopropanol (10ml.) and the mixture boiled under a Hahn partial condenser. Acetone was detected in the distillate by 2:4-dinitrophenylhydrazone reagent and when no more distilled, the reaction was stopped. After adding an excess of 50% hydrochloric acid, the solution was basified with ammonia in the presence of ammonium chloride. A blue precipitate was obtained which was insoluble in all the usual organic solvents except acetic acid.

3. Potassium borohydride.

Reduction of the ketone with this reagent in ethanol again gave the blue solid which was soluble only in acetic acid.

Ozonolysis of 2-styrylquinoline.

2-Styrylquinoline (1g.) in anhydrous ethyl acetate (50ml.) was ozonised for 0.3 hours. The identical procedure was adopted as described for the ozonolysis of 3-benzylidine-dihydro-β-quinindine. A white solid (0.1g.) was obtained which recrystallised from pyridine as white platelets, m.p. 217-218°C. (decomp.). (Found: C,75.7; H,4.7; N,9.3. $C_{20}H_{16}N_2O_2$ requires C,75.9; H,5.1; N,8.9%).

The product (50mg.) and hydroxylamine hydrochloride (170mg.) in water (1ml.), 10% sodium hydroxide (0.7ml.) and dioxan (3.5ml.) were refluxed for one hour. The volume of the solution was then reduced by one half and water added to complete the precipitation. The pale yellow solid (30mg.) was collected and recrystallised from benzene, m.p. 167-168°C. (Found: C,70.3; H,4.6; N,13.7%).

The condensation of chloral and dihydro-β-quinindine.

c.f. Alberts and Bachmann, J.A.C.S., 1935, 57, 1284.

Dihydro-β-quinindine (2.5g.) and chloral (2.5g.) in dry pyridine (20ml.) were heated on a steam bath for two hours. The reaction mixture was poured into water (100ml.) and a black oil separated which rapidly solidified. This was collected and continuously extracted with ethanol (100ml.) in a Soxhlet apparatus. The volume of the extract was reduced by one half and water then added to give a buff crystalline precipitate, (2.7g., 43%), which was recrystallised from aqueous ethanol as colourless prisms, m.p. 145-146°C. (decomp). (Found: C,53.4; H,3.9; N,3.9; Cl,31.8. $C_{14}H_{12}NOCl_3$ requires C,53.1; H,3.8; N,4.4; Cl,33.6%).

Preparation of 2:4-diphenyl-6:7-dihydro-β-pyrindine.

Stobbe and Volland, Ber, 1902, 35, 3973.

Cyclopentanone (10g.) gave 2:4-diphenyl-6:7-dihydro-β-pyrindine (3.7g.).

Condensation of 2:4-diphenyl-6:7-dihydro-β-pyrindine with benzaldehyde.

The pyrindine (2g.), benzaldehyde (0.72g.) and anhydrous zinc chloride were heated at 200°C for five hours. After cooling, the oil was dissolved in benzene and passed down an alumina column. Elution with benzene separated two yellow bands. The first consisted of starting material (m.p. and mixed m.p.) and the second yielded a pale yellow solid. Recrystallisation from petrol ether (b.p. 60-80°C.) gave pale yellow prisms (1.1g., 47%), m.p. 178-179°C.

(Found: C,90.1; H,5.8; N,3.7. $C_{27}H_{21}N$ requires C,90.2; H,5.9; N,3.9%).

Preparation of 2:4:6-triphenyl-6:7-dihydro-β-pyrindine.

Chalcone (7g.), 3-phenyl-1-cyclopentanone (5g.) and piperidine (2ml.) were mixed and allowed to stand at room temperature for one day. The solid was collected and washed with ethanol (5ml.). Recrystallisation from benzene-petrol ether (b.p. 60-80°C.) gave fine white needles (4.3g.) m.p. 148-149°C. (Found: C,85.1; H,6.7. $C_{26}H_{24}O_2$ requires C,84.8; H,6.5%).

The 1:5-diketone (2g.) and hydroxylamine hydrochloride (0.6g.) in ethanol (30ml.) were heated at 120-130°C in a sealed tube for four hours. The solvent was removed and the residue extracted with ether from an alkaline solution. After drying and removing the ether, the residue was taken up in benzene and chromatographed. Benzene eluted a reddish band which fluoresced strongly. Removal of the benzene gave an oil which slowly crystallised. Recrystallisation from methanol with carbon screening gave white prisms, m.p. 147-148°C. (Found: C,90.1; H,6.1; N,3.9. $C_{26}H_{21}N$ requires C,89.9; H,6.1; N,4.0%).

Reaction of 3-phenylcyclopentanone with β-dimethylaminopropiophenone.

c.f. Gill et al., J.A.C.S., 1952, 74, 4923.

Phenylcyclopentanone (9g.) and β-dimethylaminopropiophenone (3.5g.) were heated in an oil bath at 160°C for 0.5 hours. During this time, dimethylamine was evolved. Excess phenylcyclopentanone was then removed by distillation at reduced pressure. The residue, a red oil, was thoroughly extracted with petrol ether (b.p. 40-60°C.)

and these extracts taken to dryness. The yellow oil was dissolved in hot methanol which deposited a white solid (1.4g., 23%) on cooling. Recrystallisation from petrol ether gave colourless needles, m.p. 117-118°C. (Found: C,82.5; H,7.0. $C_{20}H_{20}O_2$ requires C,82.2; H,6.9%).

Condensation of 3:4-diphenylcyclopentenone and diethyl oxalate.

Potassium (6.6g.) was dissolved in absolute ethanol (100ml.) which was diluted with ether (100ml.). Ethyl oxalate (15.4g.) was added to the cooled solution and after 0.25 hours, diphenylcyclopentenone (24.7g.) added. The solution was left overnight then poured into water and extracted with ether. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ether. The ether was removed and the resulting oil triturated with ethanol to give a yellow crystalline solid (7g., 20%). Recrystallisation from ethanol gave yellow needles, m.p. 127-128°C. (Found: C,75.6; H,5.6. $C_{21}H_{18}O_4$ requires C,75.4; H,5.4%).

The analogous reaction with cyclopentenone gave the corresponding pyruvic ester in very poor yield. Crystallisation from methanol gave colourless prisms m.p. 60-61°C. (Found: C,59.0; H,5.5. $C_9H_{10}O_4$ requires C,59.3; H,5.5%).

Reaction of the pyruvic ester from diphenylcyclopentenone with hydrazine.

The pyruvic ester (0.8g.) and excess hydrazine hydrate were heated together in ethanol (10ml.) for five minutes. The cold solution deposited white needles (0.25g., 90%), m.p. 238-239°C and

resolidifying to a solid which did not melt up to 350°C. Oxalic dihydrazide shows the same phenomena and a mixture of the product and authentic oxalic dihydrazide showed the same properties.

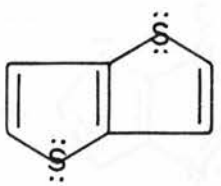
The filtrate was dissolved in ether and washed with dilute hydrochloric acid. The ether yielded a small quantity of diphenyl-cyclopentenone (m.p. and mixed m.p.). The acid washings were basified with sodium hydroxide and extracted with ether. After drying and removing the solvent, a yellow solid was obtained (0.25g.). Crystallisation from ethanol give pale yellow prisms, m.p. 165-167°C which is, however, dependent on the rate of heating. (Found: C,82.1; H,6.7; N,11.4. $C_{17}H_{17}N_2$ requires C,81.9; H,6.8; N,11.3%). This is diphenylcyclopentenone hydrazone.

SECTION II

INTRODUCTION AND DISCUSSION.

Section I described the anhydro salts derived from fused cyclopentadiene and pyridine rings. The work to be described in Section II is an introduction to the study of anhydro salts in which the pyridine ring is replaced by an aromatic, five-membered heterocyclic ring.

Pentalene would appear to possess no aromatic stability. This could be attributed on the one hand to strain derived from the fusion of two five-membered rings or on the other to a lack of suitable electron distribution and number. The strain factor does not appear to prohibit aromatic character as the substance with two fused thiophene rings, L, is known.



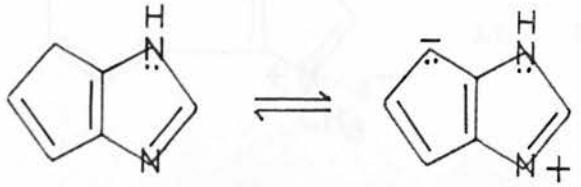
L

This structure has double bond character at the bond of ring fusion (p.8.) and ten π electrons, six from multiple bonds and four from the electron pairs of the sulphur atoms.

Imidazole exhibits typical aromatic character. It has thus been formulated as containing six π electrons as in benzene, made

up from four electrons from the double bonds united with an electron pair from the pyrrole-like =NH.

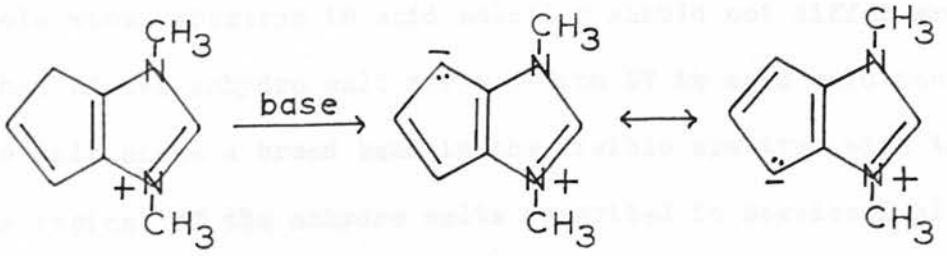
The system obtained by the fusion of cyclopentadiene and imidazole rings would be of theoretical structure LI.



(a) (b)

LI

The imidazole ring has six $\overline{\pi}$ electrons with double bond character at the bond of ring-fusion. The cyclopentadiene ring has a multiple bond and could by the loss of a proton establish a cyclopentadienyl anion. It is improbable that this would occur by a simple tautomerism (a) → (b) but could be forced by introducing a stable imidazolium ion, LII, by suitable quaternisation.

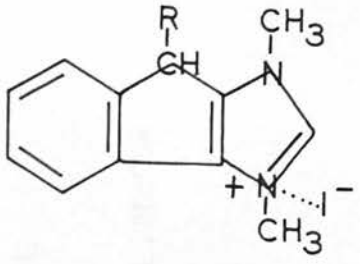


LII LIII

The latter, by the normal anhydro salt process, would yield a substance of the form LIII.

It is apparent that canonical forms of the normal cyclopentadienyl and imidazolium types may be written but there is no representation possible as a purely covalent structure.

LIV and LV have been prepared and it has been found that the latter yields a red anhydro salt which has not however been isolated.



LIV R = H

LV R = Ph

The spectra for these compounds are given in figures 15 and 16. The spectrum of LIV in alkaline solution suggests the formation of a new band due to anhydro salt formation. Since the formation of the band is incomplete, it is suggested that there exists in the solution an equilibrium between the anhydro salt and the methoiodide.

The spectrum of LV is qualitative, not quantitative. The values of $\log_{10}E$ are not actual but are derived by a comparison with the quantitative spectrum of the parent 4:5-[2':3'-(1'-phenylindeno)]-imidazole whose spectrum in acid solution should not differ greatly from that of the anhydro salt derived from LV in acid solution. The anhydro salt shows a broad band in the visible spectrum with λ_{max} = 490mμ. This is typical of the anhydro salts described in Section I although a difference is apparent in acid solution. The betaine in acid solution is intense yellow in colour and thus a broad band shifted from that of the anhydro salt to the near ultra-violet, is found. There is a further difference between the imidazole and quinindine anhydro salts. In acid solution the quinindines display a bathochromic shift whereas the imidazoles show a hypsochromic

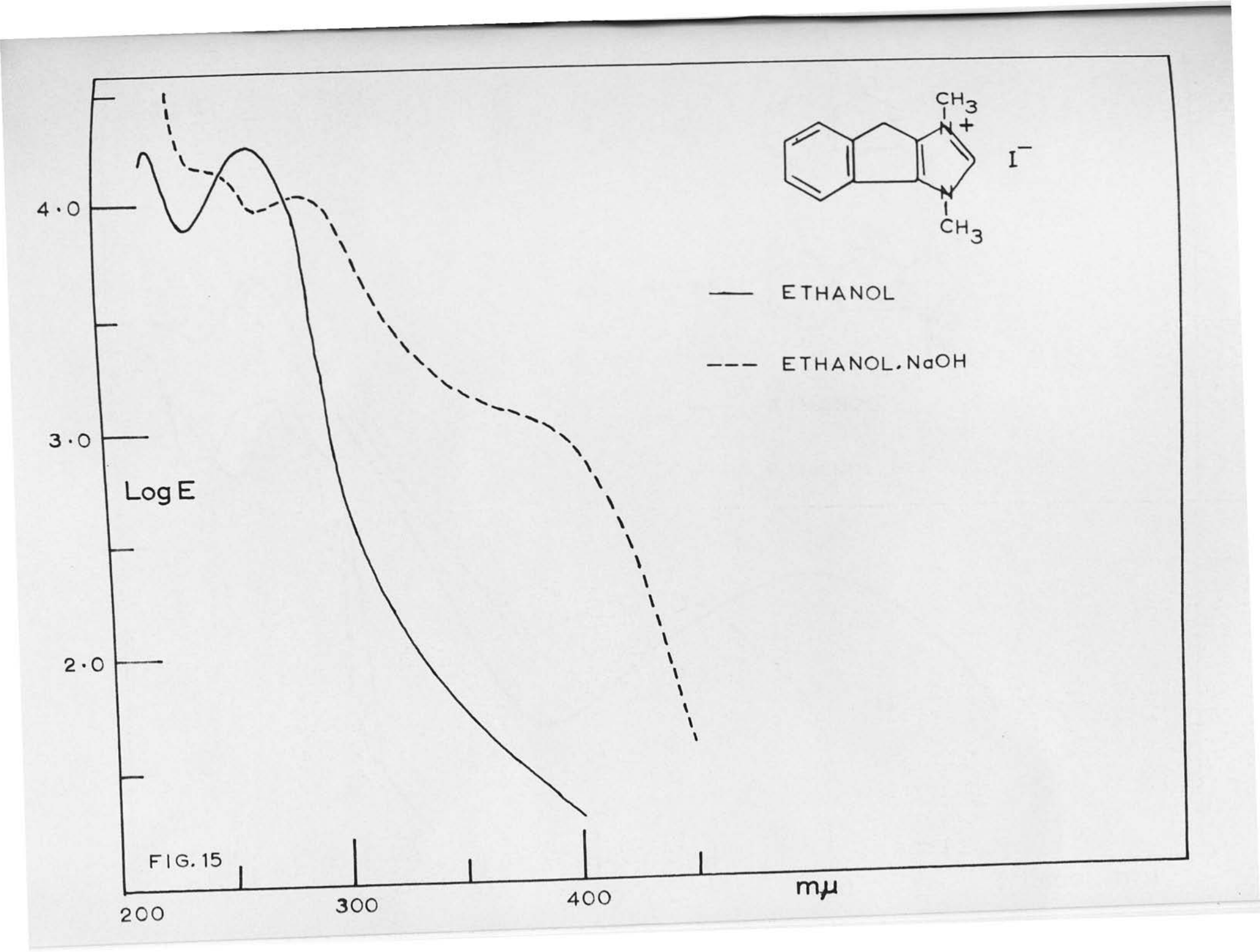


FIG. 15

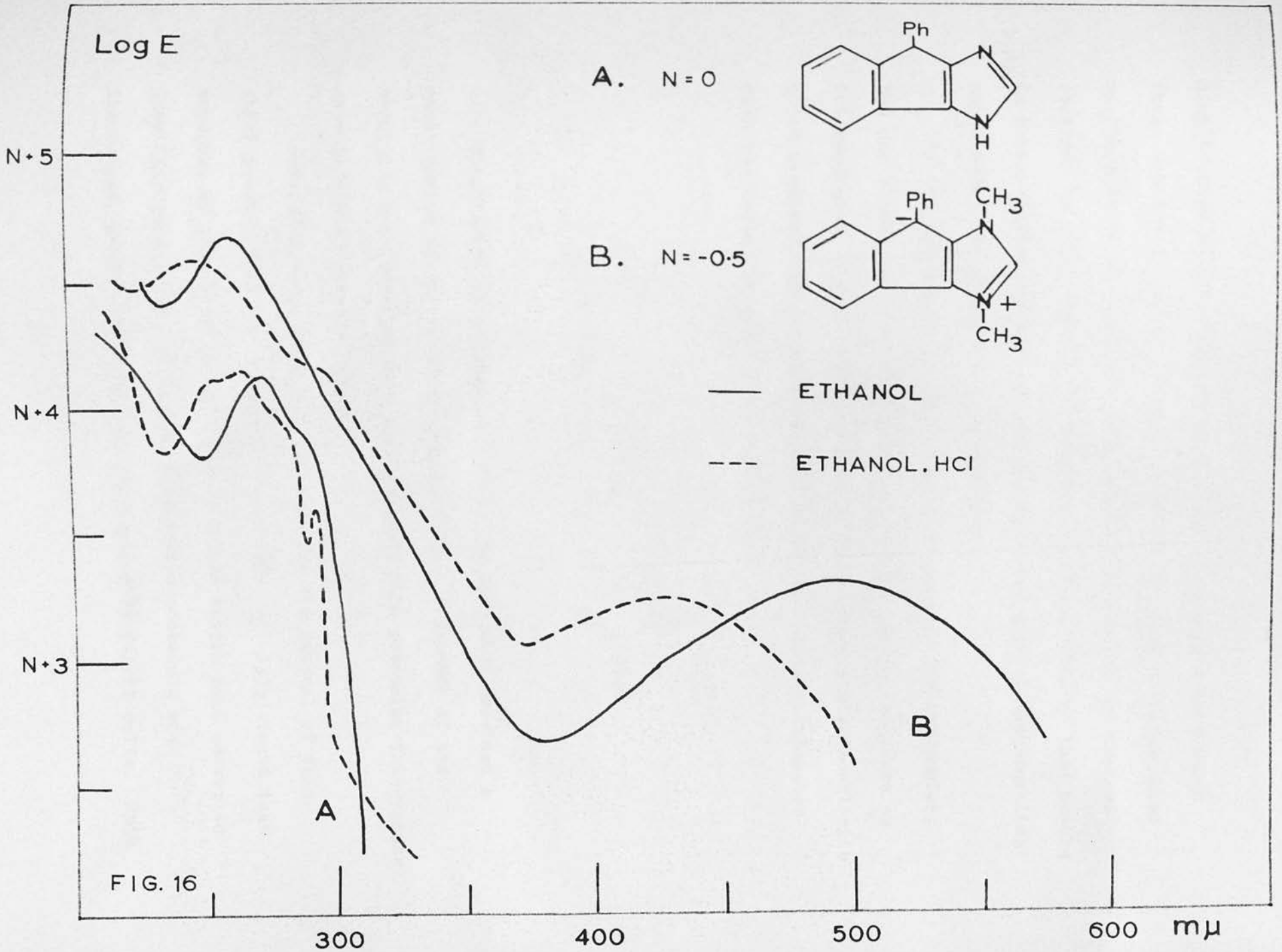
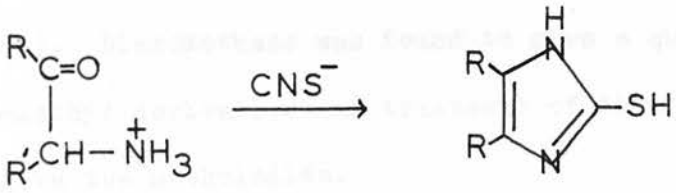

Log E
A. N = 0
Ph
N
N
H
B. N = -0·5
Ph
CH3
N
N +
CH3
ETHANOL
ETHANOL . HCl
N+5
N+4
N+3
A
B
300
400
500
600
mμ

FIG. 16

displacement in the ultra-violet. It is not possible to discuss these spectra in greater detail because of the lack of information on the spectra of imidazoles generally and especially the changes observed in acid, neutral and alkaline solution. Work of this nature is being carried out and may provide an explanation of the anomalies which were encountered in these compounds.

Of the numerous synthetic routes available to the imidazoles, the one chosen was that with 4:5-disubstituted imidazolethiones as intermediate. The reaction consists of interacting the hydrochloride of an α-aminoaldehyde, an α-aminoketone or an α-amino-β-ketoester with the potassium salt of thiocyanic acid.



Nitrosation of 1-indanone followed by reduction provided a ready source of the required α-aminoketone. Treatment of the resulting 2-amino-1-indanone hydrochloride with potassium thiocyanate gave 4:5-(2':3'-indeno)imidazole.

Several methods have been employed for the removal of this thiol group. Wohl and Marckwald (Ber., 1889, 22, 1353) found that exposure of the 2-imidazolethiones to dilute nitric acid converted them into imidazoles. Later, an alternative procedure was discovered in the oxidative desulphurisation by ferric salts. Both

these methods however have been superseded by the method of Cook, Downer and Heilbron (J.C.S., 1948, 2028) in which the thione is treated with Raney nickel in alcoholic solution.

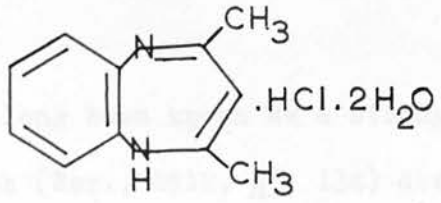
The most satisfactory yields of indenoimidazole from the thiol were obtained by the use of Raney nickel. It was found necessary, however, to employ freshly prepared Raney nickel and even better results were obtained when a stream of hydrogen was bubbled through the boiling solution.

Methylation of imidazoles has been achieved by reaction with (i), alkyl halides and subsequent treatment with silver oxide or alkali, (ii), dimethyl sulphate and (iii), diazomethane. (Chemistry of Heterocyclic Compounds, Imidazole and derivatives, Part I, p.49, by Klaus Hofmann). Diazomethane was found to give a quantitative yield of the N-methyl derivative and treatment of this compound with methyl iodide gave the methoiodide.

A similar series of reactions was carried out with 3-phenyl-1-indanone. It was thought that the phenyl group would stabilise the carbanion produced in anhydro salt formation. The reactions proceeded normally up to N-methylation. The 4:5-[2':3'-(1'-phenylindeno)] - imidazole was recovered unchanged from the reaction with diazomethane and methyl iodide. It was found necessary to employ dimethyl sulphate in benzene to effect N-methylation. Dimethylation occured to a certain extent whatever the proportion of dimethyl sulphate employed. This was indicated by the dark red colour of the chloroform extract when the solution of the methosulphate was made

basic. The N-methyl derivative could be obtained as its picrate but generally, the oil obtained from the chloroform extract was treated directly with methyl iodide. The anhydro salt was then obtained by the action of sodium carbonate on the methoiodide.

In the initial period of this research, attempts were made to make derivatives of the highly coloured compound LVI. (Thiele and Steimmig, Ber., 1907, 40, 955).



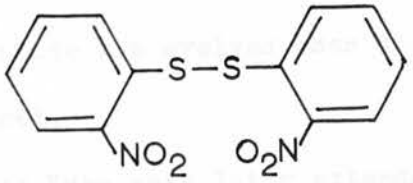
LVI

Coupling with phenyldiazonium chloride resulted in the formation of a tar from which no product could be isolated. The desired product could theoretically be prepared by the condensation of phenylazoacetylacetone and o-phenylenediamine. None of the desired product was obtained and only o-phenylenediamine dihydrochloride could be recovered.

It was therefore of interest to see whether phenylazoacetylacetone would condense to yield cyclic systems and so hydrazine was selected for study. The product was indeed 4-phenylazo-3:5-dimethylpyrazole. A solution of phenylazoacetylacetone in ethanol in the presence of excess hydrazine hydrate was inadvertently allowed to stand for two days. The characteristic orange-yellow colour of 4-phenylazo-3:5-dimethylpyrazole had disappeared and the

solution was quite colourless. Removal of the solvent gave a white crystalline precipitate which was shown to be 4-amino-3:5-dimethylpyrazole. It was also shown that aniline was the other product of the reaction. There is one reference to the reduction of azo-compounds by hydrazine (Ross and Warwick, J.C.S., 1956, 1724). Since this method of reduction was applied to a limited number of closely related compounds, it was decided to explore the generality of the reaction (Los, Stafford and Thompson, Chem. and Ind., 1956, 1277).

Hydrazine has long been known as a strong reducing agent. Möhlan, Beyschlag and Köhres (Ber., 1912, 45, 134) discovered that hydrazine was an excellent reagent for the reduction of the nitro groups in the sensitive molecule LVII.



LVII

A 90% yield of the diamine was obtained. Again, Curtius (J. prakt. Chem., 1907, 76, 233, 238, 281, 301) found that treatment of m-dinitrobenzene with hydrazine gave m-nitroaniline.

This method for the reduction of nitro groups did not however find wide usage. The reaction was found to be slow and in many cases an elevated temperature was necessary for reduction. The full value of the reaction was not established until Kuhn (J.A.C.S.,

1951, 73, 1510) discovered that the reduction of nitro-groups by hydrazine could be catalysed by either platinum or palladium catalysts. In a study of the action of hydrazine on alkyl nitrates and nitrites and aromatic nitro-compounds, Kuhn found that the nitrates and nitrites were converted quantitatively to the alcohols at room temperature in the presence of the catalyst. Aniline and m-chloroaniline were obtained in quantitative yield from their nitro-precursors under the same conditions.

Audrieth and Jolly (J. Phys. and Colloid Chem., 1951, 55, 524) studied the decomposition of hydrazine in the presence of Raney nickel. They found that nitrogen and hydrogen were the chief products. This is consistent with the observations of Kuhn who detected only nitrogen, equivalent to the amount of hydrazine employed, from the reduction of aromatic nitro-compounds. In addition, nitrous oxide was evolved when the alkyl nitrates and nitrites were reduced.

The findings of Kuhn were later extended by other workers. Balcom and Furst (J.A.C.S., 1953, 75, 4334) found that Raney nickel could replace platinum or palladium as the catalyst. Further, Dewar and Mole (J.C.S., 1956, 2556) found that in the reduction of polycyclic aromatic nitro-compounds with hydrazine, palladised charcoal was an effective catalyst.

The reduction of phenylazopyrazole was observed to be of a catalytic nature since a piece of porous tile rapidly promoted the reaction. The addition of Raney nickel to the reaction mixture

reduced the time for completion of the reaction from 24 to 0.5 hours and quantitative yields of the amine were obtained.

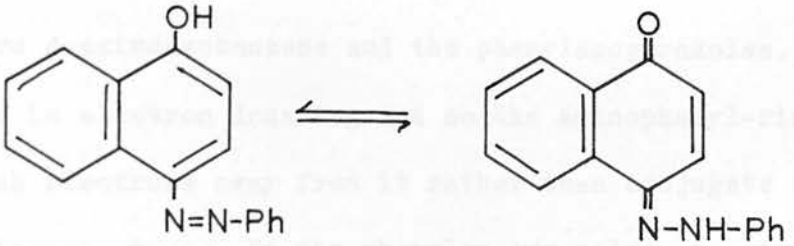
An attempt was made to establish the stoichiometry of the reaction photometrically. The high colour of the phenylazo-compounds is slowly discharged during the reaction. Erratic results were, however, obtained due to two factors. First, the reaction was shown to be a catalytic one and secondly, in dilute solution in the absence of an excess of hydrazine, the hydrazo-compound tended to re-oxidise.

The action of hydrazine on a number of azo-compounds of the benzene, naphthalene and pyridine series was examined. Three distinct cases were recognised. In the first, reaction ceases at the hydrazo-compound. This is true of azobenzeno, 3-3'dimethylazobenzene, 2-(o-chlorophenylazo)-pyridine, 4-pyridylazobenzene, 4:4'azopyridine and 3-(o-chlorophenylazo)-pyridine. Hence for azo-compounds containing only phenyl and pyridyl-type units, this is an excellent route to the hydrazo-compounds.

In the second case, the reaction causes fission of the azo-linkage to give the two amines. This is true of the phenylazopyrazoles and 4-aminoazobenzene. In order to promote reduction past the hydrazo stage, an electron releasing group on one of the rings appears to be essential. Even under the most forcing conditions, azobenzene could not be reduced to aniline.

In the third case, an electron releasing group was present but

an anomalous reaction occured. Solutions of 4-phenylazo-α-naphthol and 1-phenylazo-β-naphthol were treated with hydrazine. Although reaction of some type occured, no pure product could be isolated. An investigation by Buroway, Salem and Thompson (J.C.S., 1952, 4793) has shown that in the arylazonaphthols, there exists a tautomerism between the two forms LVIII (a) and (b).

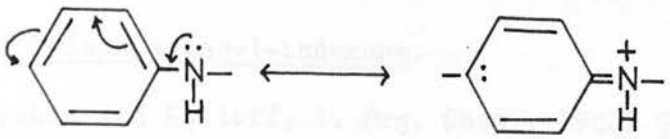


(a) (b)

LVIII

In aqueous solutions the form LVIII (b) was found to predominate i.e. the phenylhydrazone. Since the reactions with hydrazine are carried out in aqueous ethanolic solution, some reaction involving the oxygen atom is possible.

One feature is common to these azo compounds. They are all reduced. The principle difference lies in the stability of the intermediate hydrazo state to further reduction. Each nitrogen atom of the hydrazo-linkage carries a lone pair of electrons. The ability to withstand further reduction by hydrazine appears to depend on whether this lone pair of electrons can form an extended conjugated system with the terminal groups. When the terminal group is a benzene or pyridine ring, then this lone pair of electrons can conjugate with the $\overline{\pi}$ electron systems of these rings.



The only cases found in which the hydrazo-linkage is further reduced were 4-aminoazobenzene and the phenylazopyrazoles. The amino-group is electron donating and so the aminophenyl-ring will tend to push electrons away from it rather than conjugate with the hydrazo-nitrogen atoms. In the phenylazopyrazoles, no structure can be written in which there is an extended $\overline{\pi}$ electron system as in the phenylazo- or pyridylazo- compounds.

The polarographic reduction of a series of azo-compounds has been studied by Shikata and Tachi (J.C.S. Japan, 1932, 53, 834). They found that as electronegative groups were introduced into the molecule, reduction occured more readily i.e. the reduction potential was lowered. This is in general agreement with the explanation given above.

EXPERIMENTAL

Preparation of 2-isonitroso-1-indanone.

Levin, Graham and Kolloff, J. Org. Chem., 1944, 9, 384.

A solution of 1-indanone (20g.) in dry ether (300ml.) was cooled to 0°C. Butyl nitrite (18.6g.) was added to the stirred solution during one hour with the simultaneous introduction of anhydrous hydrogen chloride. The isonitroso ketone precipitated during the reaction. Benzene (200ml.) was added and the mixture cooled. The precipitate (21.2g.) was collected, washed with ether and dried. This material was used without further purification.

Preparation of 2-amino-1-indanone hydrochloride.

Levin, Graham and Kolloff, J. Org. Chem., 1944, 9, 386.

2-Isonitroso-1-indanone (14.5g.) was suspended in absolute ethanol (175ml.) containing hydrogen chloride (9.6g.). Palladised charcoal (10%, 5.3g.) was added and the flask shaken in an atmosphere of hydrogen. Two equivalents of hydrogen were taken up in two hours. After heating the reaction flask on a steam bath, the catalyst was removed and the volume of the solution reduced by one half. Ether was then added to the cold solution to give a buff precipitate of the amine hydrochloride. This was collected (15.2g.), washed with ether and used without further purification.

Preparation of 4:5-(2':3'-indeno)-imidazole-2-thione.

To 2-amino-1-indanone hydrochloride (10g.) in water (150ml.)

was added potassium thiocyanate (7.5g.). The solution was heated on a water bath for three hours during which time a pink solid had separated. This was collected and recrystallised from aqueous ethanol as pinkish, fine needles (6g., 60%) which darken at 280°C. but do not melt up to 320°C. (Found: C,63.9; H,4.5; N,14.9; S,17.2. $C_{10}H_8N_2S$ requires C,63.8; H,4.3; N,14.9; S,17.0%).

A much poorer yield of the thione is obtained when ammonium thiocyanate is substituted for the potassium salt.

Preparation of 4:5-(2':3'-indeno)-imidazole.

The indenoimidazolethione (4.5g.) and freshly prepared Raney nickel (10g.) in ethanol (200ml) were placed in a three-necked flask. The centre-neck contained a mercury-sealed stirrer while the other two contained an inlet tube for hydrogen and a condensor respectively. The solution was boiled under reflux for four hours with stirring and a steady stream of hydrogen passing through the solution. The Raney nickel was removed from the hot solution and a saturated solution of picric acid in ethanol added to the filtrate. The yellow picrate (6.2g., 72%) was collected. Recrystallisation from ethanol gave yellow needles, m.p. 217-218°C. (Found: C,50.0; H,3.0; N,17.2. $C_{16}H_{11}N_5O_7$ requires C,49.9; H,2.9; N,18.2%).

The picrate (0.5g.) in ethanol was passed down an alumina column. Ethanol separated a band which had a bright blue fluorescence in ultra-violet light. This band was eluted with ethanol and removal of the solvent gave a solid which could be crystallised from aqueous

methanol or petrol ether (b.p. 60-80°C.) as colourless prisms, m.p. 164-165°C. (Found : C,76.5; H,5.2; N,15.9. $C_{10}H_8N_2$ requires C,76.9; H,5.2, N,17.9%).

Preparation of N-methyl-4:5-(2':3'-indeno)-imidazole.

The indenoimidazolethione was converted as above to the imidazole. After removing the Raney nickel, the solution was taken to dryness. The residue was then treated three times with an excess of diazomethane in ether. After destroying the excess of diazomethane with acetic acid, the solution was washed with sodium carbonate solution and water and dried. Removal of the solvent gave a dark oil. Part of this was dissolved in ethanol and an ethanolic solution of picric acid added. The solid was collected and recrystallised from ethanol as yellow prisms, m.p. 259-260°C. (Found: C,51.0; H,3.5; N,17.8. $C_{17}H_{13}N_5O_7$ requires C,51.1; H,3.3; N,17.6%). This is the picrate of N-methyl-4:5-(2':3'-indeno)-imidazole. The yield is quantitative.

Preparation of N-methyl-4:5-(2':3'-indeno)-imidazole-N'-methoiodide.

The oily residue above was dissolved in methyl iodide and boiled under reflux for three hours. Removal of the methyl iodide left a buff solid which crystallised from ethanol in buff-coloured rosettes, m.p. 226-228°C. (Found: C,46.1; H,4.3; N,8.8; I,40.5. $C_{12}H_{13}N_2I$ requires C,46.2; H,4.2; N,9.0; I,40.7%). The yield is quantitative.

A small quantity of the methoiodide was heated on a water bath for three hours with excess methyl p-toluenesulphonate. The cold solution was extracted with ether several times and the residue crystallised from ethanol as white plates, m.p. 223-224°C. (Found: C,63.4; H,5.5; N,7.9; S,9.8. $C_{19}H_{20}N_2O_3S$ requires C,64.0; H,5.6; N,7.9; S,9.0%).

Preparation of 3-phenyl-1-indanone.

Koelsch, Hochmann and Le Claire, J.A.C.S., 1943, 65, 59. Cinnamic acid (85g.) gave 3-phenyl-1-indanone (43g., 36%).

Preparation of 2-isonitroso-3-phenyl-1-indanone.

3-Phenyl-1-indanone (40g.) was dissolved in dry ether (300ml.) and cooled to 5°C. Butyl nitrite (22.5g.) was added during one hour to the stirred solution with simultaneous introduction of anhydrous hydrogen chloride. The solution was maintained at 5°C during the addition of the butyl nitrite. The isonitroso derivative precipitated from the solution during the reaction. Benzene (200ml.) was then added and the solution filtered to give a white solid which was washed with ether and dried. Recrystallisation from ethanol gave colourless prisms (38g., 83%), m.p. 208-209°C. (Pfeiffer and Waal, Ann., 1935, 520, 185 give m.p. 201-202°C.).

Preparation of 2-amino-3-phenyl-1-indanone hydrochloride.

2-Isonitroso-3-phenyl-1-indanone (19g.) was suspended in ethanol

(250ml.) containing hydrogen chloride (9.2g.) and shaken in an atmosphere of hydrogen in the presence of palladised charcoal (10%, 5g.). Hydrogen (3.3 litres) was absorbed in ten hours. The flask was heated on a steam bath and the catalyst removed. The volume of the solution was reduced by half and excess ether added to precipitate the hydrochloride. The white solid (12.8g., 62%) was collected, washed with ether and dried. This was used without further purification.

Preparation of 4:5- /2':3'- (1'-phenylindeno) 7 imidazole-2-thione.

The amine hydrochloride (12.8g.) was dissolved in water (150ml.) and potassium thiocyanate (5g.) added. The solution was heated on a water bath for three hours during which time a pink solid had separated. This was collected and washed with water and dried. Crystallisation from ethanol gave colourless prisms (10.7g., 82%), m.p. 236-237°C. (Found: C,72.8; H,4.3; N,8.2; S,12.2. $C_{16}H_{12}N_2S$ requires C,72.8; H,4.5; N,10.6; S,12.5%).

Preparation of 4:5- /2':3'-(1'-phenylindeno) 7- imidazole.

The above thione (5g.) in ethanol (75ml.) and Raney nickel (5g.) were stirred and boiled under reflux for four hours with simultaneous introduction of hydrogen. The Raney nickel was removed from the hot solution and the volume reduced by one half. The crystalline solid which settled from the solution on cooling was recrystallised from aqueous ethanol as colourless prisms (3.3g., 76%), m.p. 251-252°C.

(Found: C,83.2; H,5.1; N,11.7. $C_{16}H_{12}N_2$ requires C,82.8; H,5.2; N,12.1%).

Methylation of 4:5- [2':3'-(1'-phenylindeno)] imidazole.

The imidazole (1g.) and dimethyl sulphate (0.5g.) in benzene (40ml.) were boiled under reflux for four hours. The benzene was removed and the residue treated with 20% sodium hydroxide solution (50ml.). Extraction with chloroform gave a deep red extract which was washed with water and dried. Removal of the solvent left a red oil.

Part of this oil was dissolved in hot ethanol and a hot, saturated solution of picric acid in ethanol added. After standing overnight a yellow solid had separated. Recrystallisation from glacial acetic acid gave yellow plates, m.p. 237-238°C. (Found: C,58.0; H,4.0; N,14.9. $C_{23}H_{17}N_5O_7$ requires C,58.1; H,3.6; N,14.7%).

Trituration of the oil with petrol-ether (b.p. 40-60°C.) caused partial crystallisation. The solid was collected and recrystallised from benzene-petrol ether as colourless needles, m.p. 198-199°C. (Found: C,82.7; H,5.4; N,11.2. $C_{17}H_{14}N_2$ requires C,83.0; H,5.7; N,11.4%). This is N-methyl-4:5- [2':3'-(1'-phenylindeno)]-imidazole.

The oil obtained from the methylation with dimethyl sulphate was treated directly with an excess of methyl iodide in benzene. An orange-coloured oil separated from the solution which could not be crystallised. This oil was treated directly with sodium carbonate

solution and extracted with chloroform. The vivid red extract was dried and the solvent removed. This again gave a red oil. Extraction of the oil with petrol ether (b.p. 40-60°C) left a small residue. This extract was taken to dryness and the residue taken up in ethanol for spectral measurements.

Coupling of benzenediazonium chloride and acetylacetone.

Bülow and Schlotterbeck, Ber., 1902, 35, 2188.

Acetyl acetone (40g.) gave phenylazoacetylacetone.(71g.)

Reactions of phenylazoacetylacetone.

1. Phenylazoacetylacetone (1g.) in ethanol (10ml.) was treated with an excess of hydrazine hydrate. The solution was warmed for five minutes and then poured into water (50ml.). The yellow precipitate was collected and recrystallised from aqueous ethanol as orange needles, m.p. 140-141°C. (Found: C,65.8; H,6.5; N,28.0. $C_{11}H_{12}N_4$ requires C,66.0; H,6.0; N,28.0%). This is 4-phenylazo-3:5-dimethyl-pyrazole.

2. Phenylazoacetylacetone (2g.) in ethanol was treated with excess hydrazine hydrate and a piece of porous plate added. Gas was evolved and the solution allowed to stand overnight. The orange colour of the solution had been discharged. The volume of the solution was reduced when a solid separated. This was collected and recrystallised from methanol as colourless prisms, m.p. 206-207°C. (Found: C,53.7; H,8.2; N,38.0. $C_5H_9N_3$ requires C,54.0; H,8.1; N,37.9%).

This compound gave the colour reactions with phenols characteristic of 4-amino-3:5-dimethylpyrazole.

This amine was diazotised in the usual manner and coupled with β-naphthol in sodium hydroxide solution. The red precipitate was collected and recrystallised from aqueous ethanol as red prisms, m.p. 262-263°C. (Found: C,67.8; H,5.2; N,20.4. $C_{15}H_{14}N_4O$ requires C,67.8; H,5.3; N,21.0%).

The filtrate from the 4-amino-3:5-dimethylpyrazole was steam-distilled and the steam-distillate treated with nitrous acid, excess being destroyed with urea. This was added to a solution of β-naphthol in sodium hydroxide solution. The red precipitate was collected and recrystallised from acetic acid, m.p. 129-130°C. This is 1-phenylazo-β-naphthol. (Lit. m.p. 131°C.)

Reaction of hydrazine hydrate with azo-compounds.

The procedure adopted for the reaction of hydrazine hydrate with all the azo-compounds is as follows. The azo-compound was dissolved in the minimum volume of ethanol and an excess of hydrazine hydrate (80%) added. The solution was then allowed to stand at room temperature until the colour of the azo-compound was discharged. A piece of porous tile promoted the reaction and generally this was added at the begining of the reaction. In most cases, the reaction mixture was poured into water and the product collected. Only for the aminopyrazoles which are soluble in water was it found necessary to remove the solvent.

1. 4-Phenylazo-3:5-diphenylpyrazole.

A white solid was obtained which was recrystallised from aqueous ethanol as colourless plates, m.p. 217-218°C. (Found: C,77.3; H,5.6; N,17.2. $C_{15}H_{13}N_3$ requires C,76.6; H,5.6; N,17.9%). This is 4-amino-3:5-diphenylpyrazole.

2. 4:4'-Azobis-3:5-dimethylpyrazole.

4-Amino-3:5-dimethylpyrazole was diazotised and coupled with acetylacetone (Morgan and Ackerman, J.C.S., 1923, 1312). The yellow product was filtered and recrystallised from aqueous ethanol, m.p. 188-189°C. (decomp.) Morgan and Ackerman give m.p. 184°C. (decomp.).

This compound was treated with an excess of hydrazine hydrate and after warming for three minutes, poured into water. The 4:4'-azobis-3:5-dimethylpyrazole crystallised from ethanol as fine yellow needles which did not melt up to 350°C.

Prolonged action of hydrazine hydrate gave a colourless solution. Removal of the solvent and recrystallisation of the residue from methanol gave colourless prisms, m.p. 206-207°C. There was no depression of the m.p. on admixture with an authentic sample of 4-amino-3:5-dimethylpyrazole.

3. Azobenzene.

A white solid was obtained which was recrystallised from aqueous ethanol as colourless plates, m.p. 129-130°C. A mixed m.p. with hydrazobenzene showed no depression.

4. 4-Aminoazobenzene.

Removal of the ethanol gave a white solid which was recrystallised from ethanol as colourless plates, m.p. 141-142°C. A mixed m.p. with p-phenylenediamine showed no depression.

5. m-Azotoluene.

Removal of the ethanol gave a colourless oil. m-Hydrazotoluene is described in the literature as a colourless oil. The oil was dissolved in water and a few drops of concentrated hydrochloric acid added. The white precipitate was collected and converted directly to the picrate in aqueous solution. The picrate was recrystallised from ethanol as yellow prisms, m.p. 230-231°C. (Found: C,46.4; H,3.5; N,16.2. $C_{26}H_{22}N_8O_{14}$ requires C,46.5; H,3.3; N,16.8%). This is the dipicrate of 2:2'-dimethylbenzidine. (Lit. m.p. 225°C.)

6. 4-Pyridylazobenzene.

A pale yellow solid was obtained which was crystallised from aqueous ethanol and recrystallised from acetone-petrol ether (b.p. 40-60°C.) as colourless prisms, m.p. 177-178°C. Koenigs et al. (Ber., 1926, 59, 324) give m.p. 171-172°C. (Found: C,71.6; H,6.0; N,20.2. $C_{11}H_{11}N_3$ requires C,71.4; H,6.0; N,22.7%).

7. 2-(o-Chlorophenylazo)-pyridine.

A white solid was obtained which was recrystallised from ethanol as colourless prisms, m.p. 103-104°C. (Found: C,60.6; H,4.9; N,18.6. $C_{11}H_{10}N_3Cl$ requires C,60.2; H,4.6; N,19.1%).

8. 3-(o-Chlorophenylazo)-pyridine.

Crystallisation of the white solid with carbon screening gave colourless prisms, m.p. 108-109°C. (Found: C,59.9; H,4.8; N,19.7. $C_{11}H_{10}N_3Cl$ requires C,60.2; H,4.6; N,19.1%).

9. 4:4'-Azobispyridine.

Recrystallisation of the white solid from aqueous ethanol gave colourless prisms m.p. 264-265°C. (Found: C,64.7; H,5.5; N,29.4. $C_{10}H_{10}N_4$ requires C,64.5; H,5.4; N,30.1%).

10. 1-Phenylazo-β-naphthol.

No pure product could be isolated from this reduction although reaction of some type had taken place.